EARLY VISUAL PROCESSING IN AGEING AND ALZHEIMER'S DISEASE

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ABSTRACT

The occipital cortex is generally reported to be spared from the pathological effects of Alzheimer's disease. The prediction of this study was therefore that the early visual processing associated with the occipital cortex would be spared in Alzheimer's disease. It was hoped that evidence for the preservation of such visual processing might provide a basis for distinguishing Alzheimer's disease from other forms of dementia that do affect the occipital cortex.

The study focused particularly on the measurement of the automatic visual processing thought to be carried out by the striate cortex. A visual analogue of the auditory mismatch negativity (an electrophysiological measure of automatic auditory processing) was developed and tested. In a test of the automatic visual stimulus change detection which underlies the production of visual mismatch negativity, individuals with Alzheimer's disease were found to have a pattern of deficits inconsistent with those associated with normal ageing. In a visual search task when the target was surrounded by relatively few distractors its automatic detection suffered no significant decrement in Alzheimer's disease compared to normal ageing. However, when large numbers of distractors surrounded the target a greater deficit in its automatic detection was found in Alzheimer's disease compared to normal ageing.

So, contrary to the prediction of the study, Alzheimer's disease was associated with a greater abnormality in early visual processing compared to that found in normal ageing. The pupillary light reflex was also tested. This reflex was found to be impaired in Alzheimer's disease compared to normal ageing, particularly in terms of the amplitude of the response. This result was interpreted as reflecting the central cholinergic dysfunction which occurs in Alzheimer's disease. It is hoped that there may be some diagnostic utility in testing vision in people with suspected Alzheimer's disease, particularly in terms of its differentiation from the effects of normal ageing.

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With special thanks to Andy, Eda and Steve.

AUTHOR'S DECLARATION

I declare that the work in this dissertation was carried out in accordance with the regulations of the University of Bristol. The work is original except where indicated by special reference in the text and no part of the dissertation has been submitted for any other degree.

Any views expressed in the dissertation are those of the author and in no way represent those of the University of Bristol.

This dissertation has not been presented to any other University for examination either in the United Kingdom or overseas.

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DATE: 22/12/98

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ETHICAL APPROVAL

The experiments described in this thesis were carried out with the informed and written consent of the young and older adults and the individuals with Alzheimer's disease to whom the procedures were explained verbally and via a printed information sheet. All procedures were approved by the Ethics Committee of Frenchay Healthcare NHS Trust.

INTRODUCTION

A. THE AIMS OF THE PRESENT STUDY

A definitive diagnosis of Alzheimer's disease can only be ascertained following invasive brain biopsy. In view of the associated morbidity and mortality risk factors associated with brain biopsy this technique is however generally precluded from use. The diagnosis of Alzheimer's disease is therefore currently based predominantly on the results of clinical examination, neuroimaging and psychometric tests.

It is sometimes difficult however, to determine whether the results of such test procedures reflect changes in brain function associated with normal ageing or whether they represent changes secondary to the onset of Alzheimer's disease. Consequently research continues in an endeavour to find increasingly specific markers for Alzheimer's disease. The tests for such potential markers of Alzheimer's disease must be non-invasive, easily applicable and well tolerated by the individual and be capable of being performed under conditions found in normal clinical practice. The present study focuses on the measurement of visual processing, in an attempt to determine whether the results from a variety of different visual tasks may be of diagnostic utility.

The pathological effect of Alzheimer's disease has been found to be significantly greater than that associated with normal ageing in the parietal, temporal and frontal cortices. In contrast however, the striate cortex has been reported as being relatively spared in Alzheimer's disease compared to normal ageing. The striate cortex has traditionally been associated with early, automatic (i.e., attention-independent) visual processing. Consequently one would expect to find that automatic visual processing is spared in AD relative to normal ageing. However it is possible that a functional deficit could occur in the apparent absence of an obvious pathological deficit. Any deficits in automatic visual function in AD compared to normal ageing, if found, may prove to be of diagnostic utility. To determine whether this could indeed be the case, the aim of the present study was to measure the functional integrity of the automatic visual processing associated with the striate cortex in both ageing and Alzheimer's disease.

In addition to the measurement of automatic visual function by the well established psychophysical technique of 'Visual Search' a further aim of the present study was to develop and test a potential new electrophysiological indicator of automatic visual function; visual mismatch negativity.

The disruption of central cholinergic function, which occurs to a much greater extent in Alzheimer's disease compared to that associated with normal ageing, involves certain neuronal relays involved in another aspect of visual function; the pupillary light reflex. A further aim of the present study was therefore to determine whether the greater deficits in cholinergic function characteristic of Alzheimer's

disease are reflected by greater abnormality in the kinetics of the pupillary light reflex compared to that found in normal ageing.

B. THE ORGANISATION OF THE THESIS.

CHAPTER ONE: provides a profile of dementia, in particular Alzheimer's disease (AD) and its comparison with the normal ageing process. The clinical, cognitive, epidemiological and aetiological features associated with AD will be described. Evidence from cognitive, biochemical, neuropathological and neuroimaging studies will provide evidence of the effects on the brain associated with both ageing and AD.

CHAPTER TWO: provides a detailed description of the anatomical and functional organisation of the visual system, emphasising in particular its modular, distributed nature and how different parts of the brain are 'specialised' to process particular aspects of the visual scene. Particular emphasis will be placed upon the aspects of automatic (attention-independent) and attention-related visual processing; the different areas of the brain associated with such processing and how the effects of ageing and AD are thought to affect such areas. Previous studies of the effects of ageing and of Alzheimer's disease on selected aspects of visual processing will be discussed.

CHAPTER THREE: describes the auditory event related potential component known as mismatch negativity which has been widely used to measure early, automatic auditory processing. The potential existence of a visual analogue of the auditory mismatch negativity is discussed in both theoretical and practical terms. The experiments performed in order to determine the existence of a visual mismatch negativity are described together with how it may be affected by ageing and Alzheimer's disease.

CHAPTER FOUR: describes the theoretical and practical aspects of the well established psychophysical technique of visual search and presents the experiments performed in order to determine the effects of ageing and Alzheimer's disease upon the automatic and attention-related visual function measured by this technique.

CHAPTER FIVE: describes the anatomical and physiological aspects of the pupillary light reflex with particular reference to the involvement of acetylcholine. The technique of infra-red pupillometry is described and the experiments performed in order to determine the effects of ageing and AD upon the pupillary light reflex are described.

SYNTHESIS: provides a brief overview of the results from the three areas of study.

CHAPTER ONE: DEMENTIA

1.1 DEMENTIA

Dementia is a syndrome that occurs in response to some kind of chronic or progressive brain disease. There is disturbance of numerous higher cortical functions leading to the development of multiple cognitive deficits including impairment in memory, thinking, orientation, comprehension, calculation, learning capacity and language. There is also a deterioration in social behaviour and personal care (World Health Organisation ICD-10, 1992 and DSM-IV 1994 in Lezak, 1995).

Dementia is usually progressive, with the mode and age at onset, course, rate of progression, pattern of neuropsychological deficits and clinical and pathological features being dependent upon the underlying aetiology.

The most prevalent causes of non-reversible dementia tend to be neurodegenerative in nature and include Alzheimer's disease, Lewy Body dementia, Parkinson's disease with dementia and Creutzfeld-Jacob disease (CJD). Other causes may be vascular in nature such as multi-infarct dementia, or the result of post-neurological insult such as traumatic head injury or cerebral anoxia. Other causes include autoimmune disease (Aids), neurosyphillis, alcohol misuse and space-occupying lesions, together with disorders of mixed aetiology (McKeith, 1997).

As life expectancy continues to increase dementia will continue to form a significant age-related pathology with the age-specific prevalence approximately doubling for every five years of age above 65 years (Tien, Felsberg, Ferris, 1993). The requirement for extensive resources to care for the increasing number of individuals with dementia has prompted a surge in research aimed at determining not only the causes of dementia but at finding preventative measures and treatments[1].

To maximise the efficacy of potential treatment and care it is imperative that the type of dementia an individual is suffering from is accurately identified[2]. However, the similarity of symptomatology, age of onset, cognitive deficits and behavioural problems between many types of dementia can often preclude their accurate diagnosis. Difficulties are also often experienced in determining the presence of the early stages of dementia from the effects associated with normal ageing. Indeed, the unequivocal diagnosis of many types of dementia in the early stages is not possible. Researchers are endeavouring therefore to develop non-invasive tests that can help to discriminate the early stages of dementia from the changes

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[1] For example, the treatment of AD with Tacrine (a cholinesterase inhibitor) which appears to be associated with stabilised or improved cognitive function in a proportion of patients (Raskind, Sadowsky, Sigmund, Beitler and Auster, 1997).

[2] (particularly as it likely that different aetiologies of dementia will require different types of treatment)

associated with normal ageing and that can discriminate between different types of dementia[3]. As Alzheimer's Disease (AD) accounts for over half of the occurrence of dementia and is therefore likely to form the major burden of dementia in the ageing population it has formed the most extensively studied of the dementia types. As the present study is concerned with the differentiation of the presence of Alzheimer's disease from the effects of normal ageing the rest of the chapter will provide a detailed overview of Alzheimer's disease.

1.2 ALZHEIMER'S DISEASE

1.2 (A) CURRENT PROTOCOLS OF DIAGNOSIS

The evaluation of the presence of probable AD in an individual follows guidelines introduced by 'The National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association' [NINCDS-ADRDA] (McKhann, Drachman, Folstein, Katzman, Price and Stadlan, 1984; McKeith, 1997). Information from patient history, physical, neurological and mental status examinations, blood tests and neuroimaging form the basis of inclusionary criteria that characterise the dementia and the exclusionary criteria that rule out other causes of the symptoms. These guidelines have resulted in 80-90% accuracy for ante-mortem clinical diagnosis of AD (as later validated by post-mortem findings) in specialised research centres. Such diagnostic accuracy has not however been achieved by many non-research based centres. (Galasko, Hansen, Katzman, Wiederholt, Masliah, Terry, Hill, Lessin and Thal, 1994; Wilcock, 1993)[4].

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[3] The earlier such abnormal changes can be detected (especially before clinical signs become apparent), the greater the potential for appropriate and effective treatment. Tests predictive of dementia are also required for those individuals who may be at familial risk or who may have an illness that has a propensity to progress to dementia.

[4] Cognitive testing may also be susceptible to confounding factors such as educational background, 'native intelligence', personality characteristics, the need for verbal responses and the subjective interpretation of some of the tests (Keilp and Prohovnik, 1995). There is often disagreement on which psychometric measurements are the most valid and reliable for clinical evaluation. Some of these factors help to account for the fact that in non-research diagnostic settings (i.e., non-specialised centres) AD may be incorrectly clinically diagnosed in as many as 25-40% of cases (Scinto, Daffner, Dressler et al., 1994).

1.2 (B) CLINICAL FEATURES

The clinical features of AD tend to be expressed in terms of high level cortical functions such as memory, learning, cognition and language[5]. Memory disturbance tends to be a universal early feature of AD and is often the first symptom to be noticed. Initially, amnesia tends to be in relation to recent events while recall of more remote occurrences remains preserved. Linguistic changes are also observed; the first often being a progressive simplification of the vocabulary used. Later in the disease signs of naming and word finding difficulties appear[6], together with an inability to formulate thoughts and word sequences Burns, Howard and Pettit (1995).

The progressive deterioration in memory and language is accompanied by a decline in intellect, personality and social behaviour. The blunting of emotions, reduction in initiative and loss of insight together with a progressive decrease in physical strength is also common. Depression may also become apparent (Burns et al., 1995).

1.2 (C) COURSE

The co-occurrence of AD-related features with those of ageing; other types of neurological disorder[7], and other types of dementia[8] make the generally insidious onset of Alzheimer's disease difficult to assess. The course of AD has however been characterised by three stages. Each stage is based on the severity of the intellectual deterioration (Lezak, 1995).

Early or stage one

Memory disturbance and disorientation are the most common presenting features of this stage. There tends to be evidence of: failing recent memory, inattentiveness, depression and irritability, word finding and naming problems, an inability to learn new skills, a loss of visuomotor ability and disturbances of mood. This stage tends to last for 2-4 years before progressing to the second stage.

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[5] The integrity of which is dependent predominantly upon the association areas of the prefrontal, temporal and posterior parietal cortex (Hof, Vogt, Bouras and Morrison, 1997).
[6] Thought to occur following the involvement with AD-related pathology of Wernicke's area in the posterior temporal lobe and angular gyrus regions) Burns et al., (1995).

[7] (such as Parkinson's disease)
[8] (Vascular and Lewy body dementia)

Stage two

This stage is characterised by a more rapid progression of cognitive decline involving many aspects of higher cerebral function. Typical features are aphasia, dyspraxia, agnosia, dyscalculia and disorientation of time and place. Behavioural problems such as aggressiveness and wandering tend to increase in severity. Motor activity may also be disturbed. Names of family members are often forgotten and people are no longer recognised.

Stage three

The final stage of AD is characterised by gross neurological dysfunction together with the loss of co-ordinated and purposeful motor activity (Arnold, Hyman, Flory et al., 1991; Lezak, 1995).

1.2 (D) EPIDEMIOLOGY

Alzheimer's disease accounts for approximately 50-70% of the typical late-onset cases of dementia (Hardy, 1997); affecting almost one in ten individuals who survive beyond the age of 65 years (Scinto et al 1994). Onset can be in middle adult life or even earlier. The prevalence increases with advancing age to an estimated 19% for individuals 75-80 years of age and 45% for individuals over 85 years. Alzheimer's disease is two to three times more common in women compared to men with men having shorter survival times than women (Moritz, Fox, Luscombe and Kraemer, 1997). Alzheimer's disease is the fourth major cause of death in the developed world after heart disease, cancer and stroke (Tien et al 1993; Fratiglioni, Viitanen, von Strauss, Tontodanati, Herlitz and Winblad, 1997).

1.2 (E) AETIOLOGY

Alzheimer's disease appears to be an aetiologically diverse condition. Genetic predisposition, head injury, infection, neurotoxins, Downs syndrome and increased paternal age, have all been implicated as causal factors, with age appearing to be the chief risk factor (Lezak, 1995). There is some evidence that age of onset of AD differentiates two possible subtypes: an early onset (pre-senile) and a late onset (senile) type (Bondareff, Harrington, Wischik et al., 1994). A greater rapidity and severity of clinical course has been associated with the early onset of AD (Bondareff et al., 1994)[9]. Both epidemiological

[9] There is some evidence that younger individuals with AD have greater problems with language function (left hemisphere dysfunction) whereas older individuals with AD have greater problems with visuospatial function (right hemisphere dysfunction). Other findings argue however, that the existence of

and molecular studies have revealed a strong genetic component underlying AD. Recent investigations have focused on the genetic variation of apolipoprotein-e (APOE)[10] gene as a determinant of the individual risk of AD. The APOE e4 allele is associated with about a two-fold increase in risk of AD in the general population aged 85 years or more (Sulkava, Kainulainen, Verkkoniemi et al 1996).

1.3 CHOLINERGIC FUNCTION

The cholinergic input to the cerebral cortex is derived mainly from the basal forebrain. The basal nucleus of Meynert provides cholinergic innervation of the neocortex. Both the medial septal nucleus and the nucleus of the diagonal band of Broca provide cholinergic supply to the hippocampus (Berg and Morris, 1990; Mesulam, Hersh, Mash et al., 1992; Mesulam and Geula, 1994). Cholinergic interneurons also form local circuits in the striatum and in the cortex itself (Fitzpatrick and Raczzkowski, 1991). The results from numerous animal and clinical studies have provided evidence that these cholinergic pathways play a vital role in the neural circuitry of learning, memory and cognition (Fibiger, 1991) and in visual information processing (Nobili and Sannita, 1997)[11].

In the healthy brain, cholinergic neurone density is highest in the limbic and paralimbic cortical area, (with particular concentration in the amygdala and hippocampus). Intermediate levels of cholinergic density are found in most sensory-motor and association cortices. The lowest cholinergic neurone density is found within the visual areas of the occipital lobe (Geula and Mesulam, 1996; Burns and Levy, 1994).

Both normal ageing and AD are associated with an increase in central cholinergic fibre loss and a reduction in central acetylcholine levels. Although the pattern of cholinergic fibre loss in normal ageing and in AD are similar, the extent of this loss is substantially greater in AD. The regions of the cortex most depleted in cholinergic function in AD are the association areas. These areas of the brain are involved in high-level cognitive functioning. By contrast, the cingulate cortex, primary visual, primary somatosensory and primary motor cortex display a relative preservation of cholinergic fibres (Geula and

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subgroups of AD is not necessarily related to age but to the extent of neuropathological change (Bondareff et al., 1994).

[10] APOE is associated with nerve regeneration regulation, neurite growth and the assembly of neuronal microtubules (Louhija, Miettinen and Kontula, 1994).

[11] It has been suggested that acetylcholine acts as a neuromodulator which affects non-specific aspects of cognition, such as arousal and attention. It has also been suggested that acetylcholine improves the signal-to-background noise ratio of acetylcholine-facilitated neurones together with preventing the activation of neurones not receiving afferent input, while enhancing synaptic interconnections among cells that are receiving input (Hasselmo and Bower, 1993).

Mesulam, 1996)[12]. Cortical afferents such as the projections from the nucleus basalis of Meynert are also depleted in AD.

Cholinergic antagonists (such as scopolamine and atropine) have been found to impair the memory of healthy older adults in a way that mimics AD. In younger adults, cholinergic antagonists have been found to interfere with learning and to cause a memory deficit reminiscent of that which arises in the course of normal ageing (Drachman and Leavitt, 1974). Atropine and scopolamine have also been shown to disrupt both the acquisition and performance of a variety of learned behaviours (Hagan and Morris, 1988; Aigner and Mishkin, 1986). Cholinergic agonists such as physostigmine appear however to enhance performance in learning and memory tasks (Hagan and Morris, 1988). In view of results such as these the deficits in cognitive function associated with AD have traditionally been interpreted as the result of its associated decrement in acetylcholine function.

It is now evident however, that AD is not simply a 'hypocholinergic state'. The view that all the symptoms of AD are predominantly a reflection of a deficit in cholinergic transmission is now difficult to sustain. The enormity of the overt structural alterations evident throughout the CNS in AD does not equate with the contribution (numerically) of acetylcholine to synaptic transmission. It is now evident that there are deficits in catecholaminergic, serotonergic, GABAergic and peptidergic neurotransmitter systems. Alzheimer's disease therefore appears instead to be a 'multisystem disorder' (Berg and Morris, 1990; Dewer and McCulloch, 1994; Turner, 1994)[13].

1.4 THE EFFECTS OF AGEING ON THE BRAIN

The brain, like all other organs, develops complex age-related changes that arise from gene-environment interactions across the lifespan.

Normal ageing is associated with neuronal degeneration, depletion and death. The dendrites of cortical pyramidal cells are also found to be much shorter, thicker and fewer in older compared to younger adults. Synaptic density in the cortex also decreases with increasing age. By the age of 80 years for

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[12] According to Geula and Mesulam, (1996) the area with the greatest loss of cholinergic innervation in Alzheimer's was the temporal lobe (a loss of >80%). Consistent with its anatomical location within the temporal lobe, the primary auditory cortex also displayed a relatively high degree of cholinergic fibre loss (69 %). The frontal, parietal and occipital association areas and paralimbic areas showed an intermediate magnitude of loss (40-75%). The anterior cingulate gyrus, primary motor, primary somatosensory and primary visual cortex displayed less than a 40% loss of cholinergic fibres.

[13] As such, it is possible that traditional pharmacological replacement strategies are unlikely to succeed in AD (unless the other changes are secondary to cholinergic loss). Synaptic information transfer between neurones mediated by neurotransmitters can be disrupted in AD at many levels in the chain, for example, abnormalities or loss of pre-synaptic elements and/or disruption at recognition sites and in second messenger systems (Dewer and McCulloch, 1994).

example, the brain has lost 15% of its weight, the cortical gyri have decreased in bulk, the sulci have widened and the ventricles are usually enlarged. It is unclear at what level of neural and functional organisation this vulnerability to ageing is expressed: individuals cells and their organelles, cortical lamina, specific nuclei, cytoarchitectonically distinct cortical regions, neurotransmitter systems, vascular networks or all the above.[14] [15] (Verkhratsky and Toescu, 1998). This age-related degeneration is accompanied by changes in information processing capabilities. All ageing brains show a reduction in cognitive function (Finch, 1994).

There does appear in fact, to be a gradient in the effects of the age-related degeneration, increasing in severity from the association to the primary sensory regions. Raz, Gunning, Head, Dupuis, McQuain, Briggs, Loken, Thornton and Acker, (1997) performed a magnetic resonance imaging (MRI) volumetry study to examine the patterns of brain ageing. They found that the pre-frontal cortex (PFC) exhibited greater sensitivity to ageing than the rest of the cerebral cortex. Other polymodal and visual association cortices (superior parietal and inferior temporal) evidenced sizeable but significantly milder age-related declines[16]. The primary visual and somatosensory cortices appear to be more resistant to the influence of age, (Kemper, 1994 and Raz, 1996) whereas primary sensory and motor areas were minimally affected[17].

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[14] The brain contains a huge population of glial cells that are responsible for the regulation of the brain micro-environment. They can also play an important role in the integrative function of neurones by controlling the concentrations of neurotransmitters and neuromodulators and thus affecting synaptic transmission and may also be affected by the ageing process.

[15] Raz, Gunning, Head, et al., (1997) suggest that the pattern of selective cortical ageing resembles the map of brain distribution of growth associated protein (GAP-43) which is considered a marker for neural plasticity and whose expression is reduced with age (Ostereicher et al., 1988). The highest concentrations of GAP-43 and consequent plasticity, have been observed in the association cortices with only a minimal amount detected in the primary sensory areas (Neve, Finch, Bird et al., 1988). Areas of greater plasticity appear therefore to be especially vulnerable to ageing. So selected cortical regions, such as the pre-frontal cortex may suffer accelerated ageing because of an impaired ability of the neurones that populate them to repair the damage and to alter their connectivity patterns. Hubbard and Squier, (1989) report that regression of the dendritic tree is another probable cause of cortical impairment with advancing age. Extensive qualitative changes including the loss of dendritic spines have been described in pyramidal cells of the temporal and frontal cortex. It has also been postulated that age-dependent alterations in the cellular mechanisms of calcium homeostasis result in sustained changes in the regulation of intracellular calcium concentrations and that this is the main cause of the neuronal degeneration, Verkhratsky and Toescu, (1998).

[16] (see also Cowell, Turetsky, Bruce et al., 1994; DeCarli, Murphy, Gillette et al., 1994; Arriagada et al., 1992 and Sullivan et al., 1995, for similar findings).

[17] Selectivity of brain ageing may have evolutionary and ontogenic underpinnings. The most age-sensitive regions in the neocortex are those which form the latest phylogenetic additions to the brain, whereas the primary sensory areas, which are less sensitive to age-related changes, have changed little in the course of mammalian evolution (Armstrong et al., 1990). In early development, age-sensitive cortical regions also tend to mature later than the areas relatively spared by ageing. Thus according to

1.5 NEUROFIBRILLARY TANGLES AND SENILE PLAQUES IN NORMAL AGEING

The normal ageing of the brain is accompanied by the development of abnormal protein deposits throughout the cortex, particularly neurofibrillary tangles and senile plaques. The formation of these pathological structures and how they lead to the gradual reduction in the number of neurones and synapses associated with the cognitive decline typical of AD is not yet fully understood.

Neurofibrillary tangles (NFTs) are aggregates of abnormal protein deposits inside the cell body of neurones[18]; the major component being a protein known as Tau (Hardy, 1997; Burns et al., 1995). NFTs are a sign of neuronal cytoskeletal degeneration and tend to occur predominantly in the pyramidal cells of the neocortex (Hof and Morrison 1990). In normal ageing NFTs are found predominantly in the hippocampus, amygdala and parahippocampal gyrus (i.e., the medial temporal structures, Burns et al., 1995).

Senile plaques are accumulations of extracellular filamentous protein aggregates which occur particularly in areas of the brain containing axons. Senile plaques consist of an amyloid core (which does not occur naturally in the brain) and appear to be the debris deposited by degenerating neurones. Senile plaques (SPs) have a broader and more varied distribution than NFTs.

The degeneration of the organisation of the cortical architecture, the loss of synapses and the interference with neuronal transmission associated with NFTs and SPs is thought to result in the loss of functional integrity. A reduction in blood flow, oxygen consumption and neurotransmitter function also occurs with increasing age (Burns et al., 1995; Cummings and Cotman, 1995).

1.6 THE EFFECTS OF ALZHEIMER'S DISEASE ON THE BRAIN

Senile plaques and neurofibrillary tangles constitute the two 'traditional hallmark' features of AD (Smith, Sayre, Monnier and Perry, 1995)[19] . The NFTs and SPs in AD show a similar pattern of distribution as they do in normal ageing. The density of NFTs and SPs in AD in some areas of the brain

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Raz et al., (1997) increased vulnerability may be the price for increased developmental malleability of some cortical areas.

[18] (i.e., intracellular).

[19] There is emerging evidence for a new type of lesion; 'amyplaques' which resemble amyloid plaques from the outside but inside lack the core of beta-amyloid (Wade and Roush, 1997).

is however much greater than that found in normal ageing with subsequently greater consequences[20]. The pathological features of AD are distributed unevenly in the cerebral cortex. There appears to be a sequence of areas affected. The neurons of the entorhinal region of the temporal lobe[21] are the first neurones to show the development of intraneural changes, followed by the neurons of the hippocampus, the association areas of the cortex and eventually, in the late stages of the disease, the neurons of primary areas of the cortex (Arriagada et al., 1992); (Brääk and Brääk, 1994).

1.7 ALZHEIMER'S DISEASE AND NEUROFIBRILLARY TANGLES

In AD, the greatest NFT loads are found predominantly in the hippocampus, the temporal[22], the parietal and the frontal cortex (Jöbst, Smith, Szatmari et al., 1992; Armstrong, Nocklin, Sumi et al., 1990; Hof, Bierer, Perl et al., 1992), with the numbers being significantly greater than those found in normal ageing. The occurrence of NFTs in the projection neurones of the limbic and association cortices is thought to disrupt the flow of information along axons linking association cortices and the limbic cortical areas[23] (Brääk and Brääk, 1991; Arriagada et al., 1992; Gomez-Isla, Hollister, West et al., 1997). The NFTs in the limbic and association cortices are accompanied by NFTs in the neurones of subcortical nuclei that project to these regions, such as the cholinergic forebrain complex (Selkoe, 1996). NFTs specifically affect neurones in layers II, III and V in association cortex, corresponding to feedforward and feedback projections (Arnold, Hyman, Flory et al., 1991; Hof and Morrison, 1990). In comparison to the above areas of the brain the occipital cortex, particularly the striate region, is relatively spared from NFTs[24] (Schlotterer, Moscovitch and Crapper-McLachlan, 1983; Benson, Cummings and Kuhl,1981; Mendez, et al.,1990; Lewis, Campbell, Terry et al., 1987.

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[20] As a result of the reduction in functional integrity associated with the pathological processes accompanying ageing and AD, it appears that the areas of the brain which have the greatest pathological loading of such features will suffer the greatest deficits in their processing.

[21] The entorhinal cortex (especially layers II and IV) is amongst the first and most severely affected regions of the temporal lobe structures (Brääk and Brääk, 1992). There is also destruction of the pathway from the entorhinal cortex which receives input from higher order multimodal and sensory-specific association cortices and transmits that information to the hippocampus, (Goldsmith and Joyce, 1995) resulting in the memory deficits so characteristic of AD.

[22] (particularly the medial temporal regions and the superior temporal sulcus which is a high-order association cortex that receives input from multiple modalities, including vision (Gomez-Isla et al 1997; Arnold et al., 1991 and Arriagada et al., 1992)

[23] (in the medial temporal lobe)

[24] The cells in the cerebellum also remain relatively unaffected by NFTs (Joachim, Mori and Selkoe, 1989) as are the cells in the primary somatosensory area.

1.8 ALZHEIMER'S DISEASE AND SENILE PLAQUES

The density of SPs in AD is generally greater than that found in normal ageing. Senile plaques (SPs) have a broader and more varied distribution than NFTs but like NFTs tend to be more numerous in the temporal, parietal and frontal lobes and the limbic structures than in the primary motor and somatosensory areas (see Della Sala, Muggia, Spinnler et al., 1995 for a review). However, unlike NFTs substantial numbers of SPs have been found in the striate cortex (Brääk and Brääk,1986; Arnold et al.,1991). Kuljis and Tikoo, (1997) also found a 'laminar predilection' in the pattern of SP distribution in the striate cortex, with a higher density in layers I to III and V and a relative paucity in layers IV and VI (these layers of the striate cortex are discussed in chapter two).

The amyloidcentric theory of AD proposes that amyloid plaque deposition triggers a neurotoxic cascade, thereby causing neurodegeneration and AD (Hardy, 1997 and Selkoe, 1996). Several lines of evidence however suggest that amyloid might not be the primary causative agent for the development of AD neurodegeneration. High levels of SPs have generally appeared not to cause functional deficit in the area where they are found. In addition no correlation has been found between amyloid deposition and the degree of dementia. Research has tended to indicate that the number of SPs in the cerebral cortex remains stable independently of the duration of the illness. Although there is some correlation of SPs with the degree of cognitive impairment, the number of NFTs correlates more closely with the severity of dementia (Arriagada et al., 1992; Berg, McKeek, Muller et al., 1993; Hyman, Arriagada, Van-Hoesen et al., 1993; Nagy, Esiri and Jobst, 1995; Gomez-Isla et al., 1997). There appears to be a closer relationship between NFT accumulation and clinical evolution of the disease than with SPs. It is also not unusual to find levels of cortical amyloid depositions in the brain of healthy older adults that are as high as those seen in older adults with AD (Arriagada et al., 1992; Neve and Robakis, 1998). So the presence of NFTs qualitatively and quantitatively matches the clinical (particularly cognitive) deficits of AD better than the number and distribution of SPs (Wilcock and Esiri, 1982; McKee, Kosik and Kowall, 1991 and Gomez-Isla et al., 1997)[25]. The precise functional impact of SPs remains unclear.

1.9 CORTICO-CORTICAL ASSOCIATION NEURONS AND ALZHEIMER'S DISEASE

In addition to the evidence for the predilection of certain anatomical regions of the brain for pathological change in normal ageing and AD a predilection for certain types of neurone is apparent (Dewer and

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[25] Kuljis and Tikoo, (1997) suggest that part of the controversy regarding both SP and NFT distribution may be due to the relative lack of sensitivity of the methods sometimes used to reveal AD-associated lesions.

McCulloch, 1994). Jobst et al., (1992); Hof and Morrison, (1990); Turner, (1994) reported that the neurones that are principally and progressively affected in AD are predominantly the projection or cortico-cortical association neurones. These are the axons of pyramidal cells, which give rise to the associational projections within the hemispheres that interconnect association areas of the cortex.

These cortico-cortical connections form a massive communication system which is likely to mediate elementary sensory processes as well as complex cognitive processes such as learning and memory. Such projection neurones, for example in sensory cortices, originate and terminate in specific layers depending on their destination (Maunsell and Van Essen, 1983). Forward connections[26] originate in cortices concerned with elementary sensory processing and terminate in areas concerned with the more complex aspects of processing (Rockland and Van Hoesen, 1994; O'Neil, 1991).

Pearson, Esiri, Hiorns et al., (1985); Kumar, Schapiro, Grady et al., (1991) and Arriagada et al., (1992) reported a predilection for pyramidal cells to be involved in AD, particularly in layers III and V of the cortex (which represent the origin of the cortico-cortical association connections). This was found to be particularly evident in the frontal cortex, the inferior temporal cortex and layer III of area V2 (Davies, Mann and Sumpter, 1987). There appeared however to be less of a loss in layer III of area V1, the primary or striate visual cortex (Morrison, Hof, Campbell et al., 1990).

There is a marked loss in AD compared to normal ageing of the large pyramidal cells that provide connections between association cortices and with certain subcortical nuclei that innervate the cerebral cortex (Harrington and Wischik,1994). Morrison et al., (1990) have demonstrated a striking regional and laminar correlation between NFT distribution and the origins and terminations of long cortico-cortical and key hippocampal projections. In fact, Brääk and Brääk, (1986) suggested that NFT formation may only occur in pyramidal cells in the cortex as several classes of non-pyramidal interneurons have been shown to be resistant to AD pathology.

It is the pyramidal neurones that mediate the bulk of associative processing in the cortex, their degeneration therefore results in some degree of 'cortical disconnection' which has a profound influence on cognitive function (Barbas and Rempel-Clower,1997).

Alzheimer's disease has indeed been characterised as a 'cortico-cortical disconnection syndrome' by Morrison, Scherr, Lewis et al., (1986). It is thought that this fundamental disconnection of the cortex is the cause of the greater deficit in higher-level processing in AD compared to that found in normal ageing. However, it appears that all cortico-cortical systems are not equally vulnerable, with short projections from primary sensory areas to adjacent secondary sensory areas being more resistant to degeneration than long association pathways (Hof and Morrison, 1990; Lewis et al., 1987.

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[26] proceed away from the primary cortices

1.10 OTHER PATHOLOGICAL FACTORS AFFECTING THE BRAIN IN ALZHEIMER'S DISEASE

AD is also characterised by synapse loss, particularly in the frontal, inferior parietal, superior temporal and superior middle temporal cortex. Although the degenerative process primarily affects the grey matter, the white matter may not be spared; infarctions of the white matter correspond to partial loss of myelin sheaths, axons and oligodenrocytes (Burns and Levy, 1994). Substantial cell loss is also found in the subcortical nuclei; the amygdala, the nucleus basalis of Meynert, the nucleus raphe and the locus coeruleus, thus affecting the cortical afferents (Katzman 1986).

AD also appears to be associated with greater deficits in energy metabolism compared to normal ageing. Dysfunction of the mitochondrial electron transport chain proteins (which disrupts the neurones energy supply) has been associated with AD. AD is also associated with changes in cell membrane composition which results in impaired neurotransmitter and signal transduction function (Roth, Joseph and Mason, 1995).

1.11 CONTRAST SENSITIVITY FUNCTION AND ALZHEIMER'S DISEASE

The measurement of contrast sensitivity function (CSF)[27] has often been applied to the testing of cortical integrity in AD compared to that in normal ageing.. Decrements in CSF occur with lesions of the occipital, temporal and parietal cortices. Occipital and occipitotemporal damage appears to be associated especially with loss at high spatial frequencies, whereas temporal and parietal damage is related to loss at lower frequencies (Cronin-Golomb, Corkin, Rizzo et al. 1991). The few studies of contrast sensitivity in AD have however yielded inconsistent results. For example, Schlotterer et al., (1983) and Wright, Drasdo and Harding, (1987) reported normal CSF in AD. Cronin-Golomb et al., (1991) however found it to be impaired; only low spatial frequency contrast sensitivity was significantly different between individuals with AD and healthy controls. Low spatial frequency loss was also correlated with the severity of dementia. According to Cronin-Golomb et al., this indicated damage to the temporal or parietal areas. A finding consistent therefore with pathological studies. However, Hutton, Morris, Elias and Poston (1993) demonstrated a generalised depression of the spatial contrast sensitivity in mild to moderate AD with greater effects at high spatial frequencies, therefore indicating damage to the

[27] Contrast sensitivity is the reciprocal of the contrast threshold for a particular spatial frequency and contrast sensitivity functions are log-plots of contrast sensitivity for several spatial frequencies (Hutton, Morris, Elias and Poston 1993). Under ideal conditions humans can distinguish gratings of spatial frequencies between 0.5 to 50 cycles per degree from a uniform grey stimulus; the greatest sensitivity occurring at about 6 cycles per degree.

occipital regions. Such a result indicates the possibility of functional deficits occurring in the absence of obvious pathological change.

1.12 NEUROIMAGING IN AGEING AND ALZHEIMER'S DISEASE

Neuroimaging has provided further evidence regarding the extent to which the structure and function are affected in AD compared to normal ageing.

1.12(A) ANATOMICAL IMAGING

The neuronal degeneration and cell loss associated with AD appears primarily as atrophy in anatomical imaging such as computerised tomography (CT) and magnetic resonance imaging (MRI).

Areas of the brain found to be particularly affected by atrophy in AD compared to healthy ageing have included: the lateral and third ventricles (Förstl, Hentschel, Sattel et al., 1995); the hippocampus; the frontoparietal region; the temporal lobes (Jobst et al., 1992; Jernigan, Archibald, Berhow et al., 1991), in particular the medial temporal lobe (Jobst, Smith, Szatmari et al., 1992 and Jack, Peterson, O'Brien and Tangalos, 1992) and the basal ganglia (Jernigan et al 1991). Such findings agree with the findings from histopathological studies which describe a similar distribution of NFTs and SPs.

1.12(B) FUNCTIONAL IMAGING

Functional imaging is usually in the form of positron emission tomography (PET) or single photon emission computerised tomography (SPECT). Both techniques use radioactive markers combined with sophisticated detectors to derive pictures of brain metabolic activity. In such imaging, neuronal degeneration and loss appear primarily as decreased physiological function as measured by regional cerebral blood flow[28]. Functional imaging is able to reveal the more subtle changes that occur independently from or before the structural changes, i.e., before they become apparent on anatomical imaging (Chertkow and Bub, 1994).

Functional imaging studies have revealed that the following areas are particularly reduced in function in AD compared to normal ageing: the **Temporal lobes** (Costa, Ell, Burns, Philpot and Levy, 1988; Goto et al., 1993; Eberling, Jagust, Reed et al., 1992; Wolfe, Reed, Eberling et al., 1995 and Tien et al., 1993), **the Parietal lobes** (Martin, Browers and Lalonde, 1986; Kumar et al., 1991; O'Brien, Eagger,

[28] (which is interpreted as reflecting local synaptic activity, or regional glucose or oxygen metabolism).

Syed et al., 1992; Goto et al., 1993; Meyer, Muramatsu and Mortel, 1995 and Waldemar, 1995), **the Frontal cortex** (Tien et al., 1993; O'Brien et al., 1992; Goto et al 1993; Hashikawa, Matsumoto, Moriwaki et al., 1995; Tedeschi, Bertolino, Lundbom et al., 1996; Iyo, Namba, Fukushi et al., 1997 and Marco, 1995).

Neuroimaging studies also indicate that in the early stages of AD, it is mainly the temporal and parietal lobes which are affected with the frontal lobes becoming progressively affected as the disease advances (Wolfe et al., 1995; Tien et al., 1993; Jagust, Reed, Seab et al., 1990; Golan, Kremer, Freedman et al., 1996 and Smith et al, 1992). Duara, Barber, Loewenstein et al., (1990) and Rappaport, Howitz, Grady et al., (1991) however, report that the frontal lobe can be affected in early and preclinical stages of AD. Such studies have also revealed that the primary sensory areas, in particular the primary visual cortex (striate cortex) is among the areas least affected by AD (Goto et al., 1993; Mendez et al.,(a & b) 1990; Geaney and Abou-Saleh, 1990; Herholtz, 1995 and Mielke, Kessler, Fink et al., (1995).

These findings suggest therefore that the areas found to be predominantly affected by large numbers of NFTs and SPs in AD are those which show the greatest reduction in functional integrity.

Of particular interest to the present study was the finding by Smith et al., (1992) who found that in the most advanced stages of AD, the metabolic deficits in the regions most affected in the early stages (i.e., the temporal, parietal and frontal areas), became more pronounced, but deficits in the occipital cortex, which was only mildly, if at all affected in the early stages did not significantly worsen. There appears therefore to be relative sparing of the visual cortex until the later, end-stages of the disease. Other brain areas that appear (using neuroimaging techniques) to be little affected by AD are the brainstem, cerebellum and the primary motor area (Geaney and Abou-Saleh, 1990). Such findings correspond to the general results of histological, biochemical and cognitive tests of brain function.

1.13 ALZHEIMER'S DISEASE AND THE AREAS OF THE BRAIN ASSOCIATED WITH VISUAL PROCESSING.

The results of multidisciplinary studies all agree that there is a marked difference in the extent to which specific areas of the brain are affected by AD. This difference in pathological load and degeneration is expressed particularly well in the visual system. The areas associated with the higher-level and attention-related aspects of visual processing include the parietal and temporal cortices. The effects of AD on both of these areas is far greater than the effects of normal ageing. This is reflected in the finding of greater deficits in higher-level and attention-related visual function in AD compared to normal ageing (Lezak, 1995).

By comparison, the areas involved with the early or automatic aspects of visual processing include the occipital cortex, particularly the striate cortex[29]. The effects of AD on these areas (particularly in terms of NFT density) are reported to be minor in comparison to the effects of normal ageing. Consequently the occipital and striate cortex is generally referred to as being 'spared' in AD. One would expect therefore that there would be little if any, deficit in early or automatic visual processing in AD compared to normal ageing. Visual evoked potential studies have provided some evidence for the anatomical and functional integrity of the striate cortex in AD. Generally however, very few studies have attempted to characterise the functional integrity of the striate cortex in terms of its automatic function.

One of the aims of the present study was therefore to characterise the effects of AD compared to normal ageing upon automatic visual processing. It was hoped that such research would complement the findings from studies of higher level visual processing and therefore provide a wider picture of the effects of both ageing and AD upon visual processing. If indeed a specific pattern of AD-related deficits does emerge then tests of visual function may have the potential for use as peripheral markers for the differential diagnosis of AD from ageing and from other types of dementia.

Before going on to describe the tests used to measure visual function in AD and in ageing in the present study, the following chapter will describe the anatomical and functional architecture of the visual system in greater detail. Specific detail will be applied to the description of automatic and attention-related aspects of visual processing.

[29] (the primary visual cortex or V1)

CHAPTER TWO: FUNCTIONAL ORGANISATION OF THE VISUAL SYSTEM

2.1 THE FUNCTIONAL ANATOMY OF THE VISUAL SYSTEM

Evidence for the way in which visual information is processed in humans has been obtained from a variety of techniques. Anatomical tracing of nerve tracts, electrophysiology, psychophysics, neuroimaging and clinical lesion studies have all been employed in determining the functional anatomy of the visual system. A significant body of evidence has also been derived from the study of laboratory macaque monkeys, which being sufficiently phylogenetically similar to humans, has enabled the function of many aspects of the human visual system to be inferred from analogous anatomy.

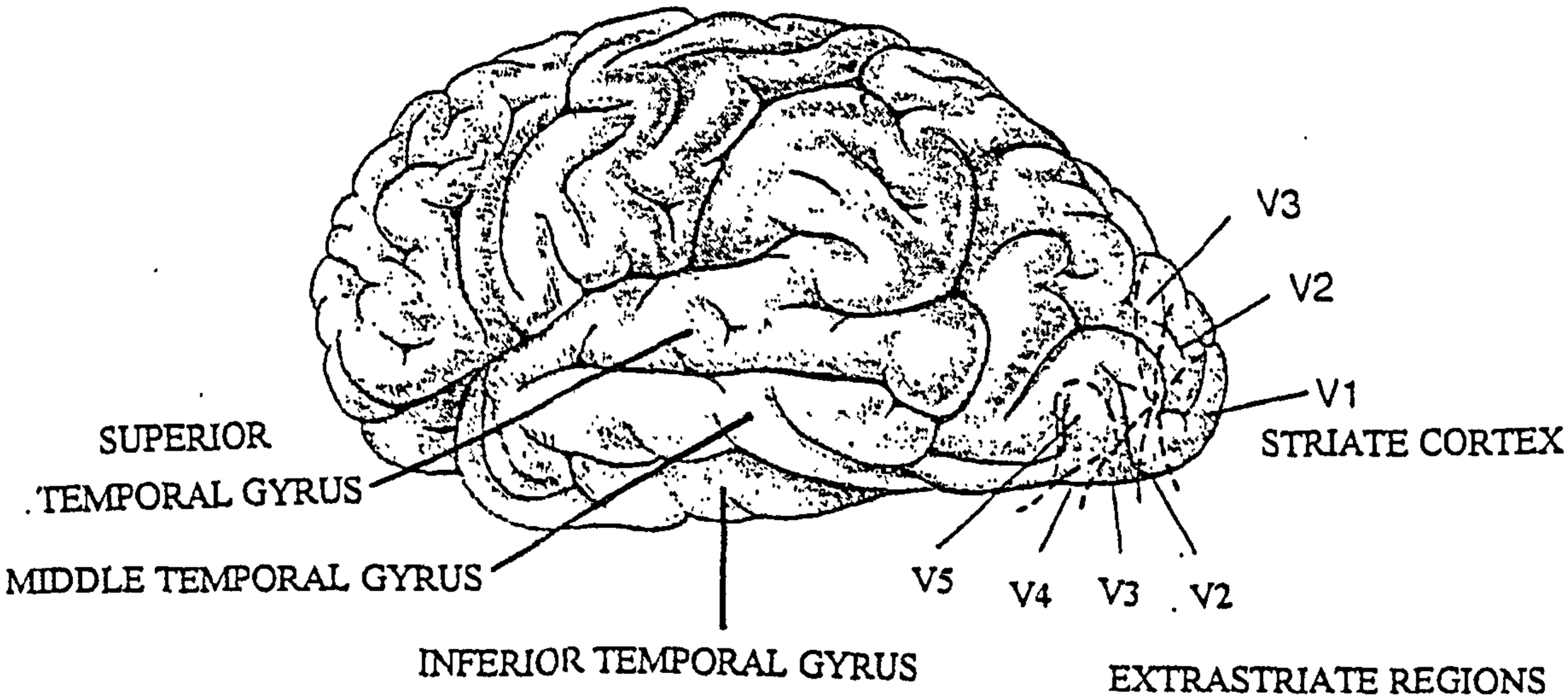
The results of such research have indicated the distributed, but highly interconnected nature of visual processing. The numerous regions of the brain associated with visual processing tend to differ in terms of connectivity, physiology, anatomy, biochemistry and importantly, function. This multi-distributed but highly interconnected organisation appears to facilitate the concurrent and therefore very rapid, extraction of the different types of information contained within the visual scene. The re-combination of the results from this processing forms our percept of the visual scene.

The identification of the type of visual function that occurs in a particular region of the brain enables the integrity of that particular region to be assessed. Of particular interest to the present study is the processing mediated by the occipital cortex. Figure one illustrates some of the regions associated with visual processing in the occipital cortex.

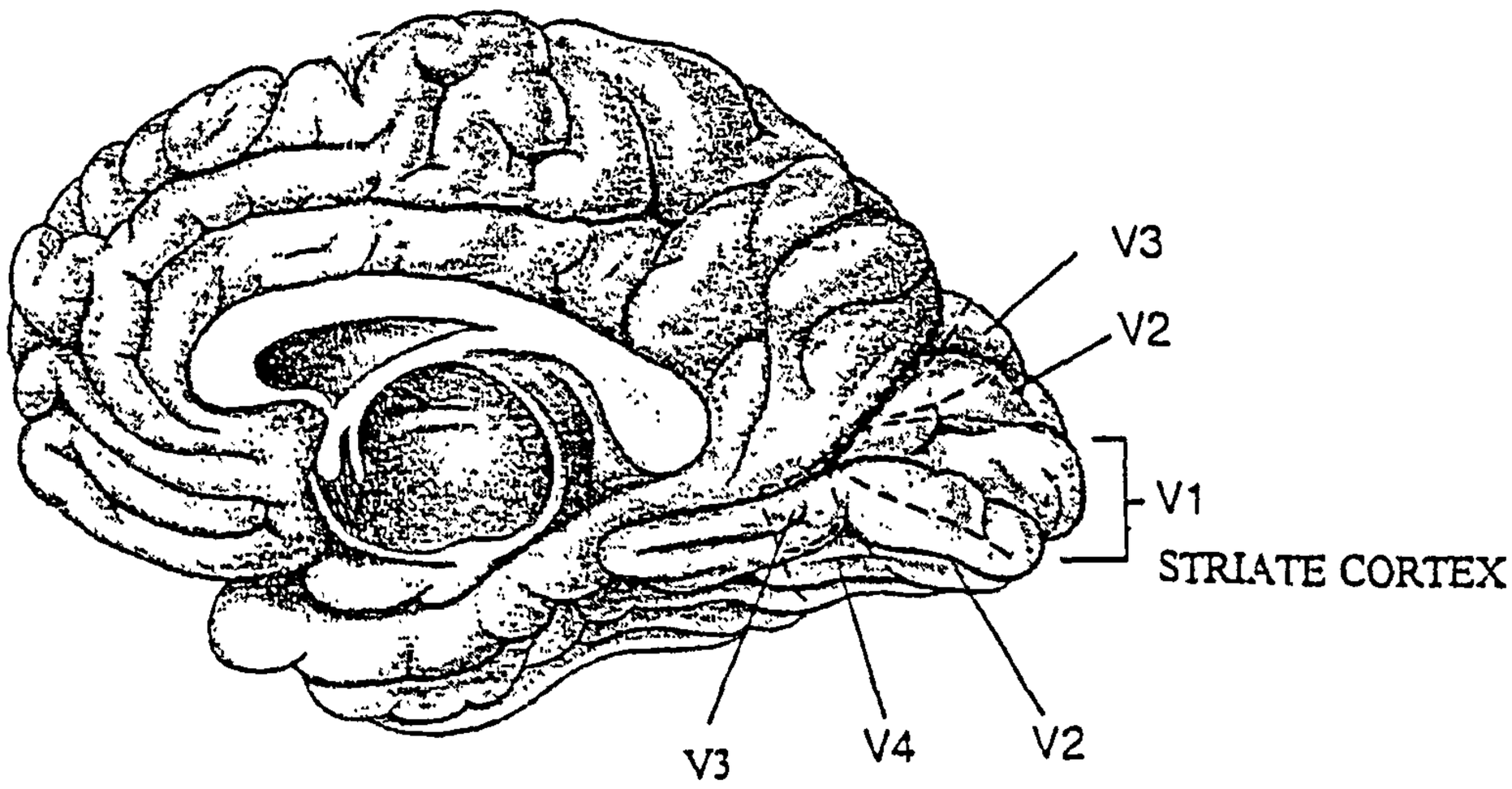
Figure 2.1 Human Cortical Visual Areas[30]

(Adapted from Kolb and Whishaw, 1996; p 245)

A: LATERAL VIEW OF CORTICAL VISUAL FUNCTIONAL AREAS



B: MEDIAL VIEW OF CORTICAL VISUAL FUNCTIONAL AREAS



30 These are the 'probable' locations of V3, V4 and V5.

2.2 LEVELS OF VISUAL PROCESSING

It is generally accepted that visual information is processed in multiple stages and at various levels of complexity. The retinal image undergoes increasingly complex transformations from a relatively simple representation in the striate cortex (V1) to a more complex representation in higher order processing areas, such as the parietal and temporal cortices; resulting ultimately in visual perception (Tanaka, 1993). Early evidence for the increasingly complex analysis from the retina to the striate cortex and beyond was obtained by Hubel and Wiesel (1959, 1962, 1968, 1970).

The initial stages of visual processing are sensory or low-level in nature; involving the active extraction and neural representation of the basic features of which the visual scene is composed. These basic features include orientation, spatial frequency, velocity and spectral composition. The initial extraction of these basic features is generally acknowledged to commence in the retina and to continue in the striate cortex. The extraction of the different features, often mediated by distinct neuronal populations, occurs in parallel and is consequently a rapid process. The receptive field properties of neurones in the striate cortex (to be described in section 2.12) display a functional architecture commensurate with such processing and the subsequent transfer of this information to other visual processing areas.

From the striate cortex, processing continues throughout the extrastriate visual areas of V2, V3, V4 and V5, and the visual association areas of the parietal, temporal and frontal cortices. Each area appears to be specialised for the processing of specific features abstracted by the striate cortex. This subsequent processing is not strictly hierarchical[31]; it does not occur in a step-wise manner along contiguous visual areas and levels of processing. The increasingly complex processing of visual information depends instead upon a system of combined hierarchical and parallel processing with multistage integration and feedback (DeYoe and Van Essen, 1988; Livingstone and Hubel, 1988; Zeki and Shipp, 1988; Desimone and Ungerleider, 1989; Merigan, Nealey and Maunsell, 1993; Van Essen and DeYoe, 1995).

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[31] Evidence for hierarchical processing has been presented by Elston and Rosa, (1997) who by comparing dendritic fields of neurons in the cortical layer at different levels of a physiologically defined [visual processing] stream, indicated changes in pyramidal cell morphology between functionally related areas. For example, the basal dendritic territories of pyramidal neurons at an intermediate level of the occipitotemporal pathway (V4) are larger than those in lower areas (i.e. V1 and V2), but less than the parietal area and and the inferior temporal cortex. This trend has been interpreted as a correlate of the anatomical hierarchy of processing, whereby the more widespread intrinsic connections coupled with the larger centre-to-centre spacing reflects the more global computational roles proposed for higher order visual areas.

2.3 AREAS OF THE BRAIN INVOLVED IN VISUAL PROCESSING AND THEIR FUNCTION

2.3 (A) THE RETINA

Visual information processing is initiated when energy in the form of light impinges on the retina. The resulting intensity distribution triggers an electro-chemical process within the retinal rod and cone photoreceptors leading to the transduction or encoding of light in terms of electrical potentials[32] (Van Essen and De Yoe, 1995).

The activity produced by the action of light on the photoreceptors projects, via the retinal bipolar cells, to the retinal ganglion cells[33]. By virtue of their receptive field[34] properties the retinal ganglion cells process the information contained within the activity from the photoreceptors and signal the presence of certain features[35] in the visual scene.

The type of information extracted by the retinal ganglion cells has been determined physiologically by measuring their response characteristics to the presence of different visual features in their receptive fields. Such research has highlighted the existence of several retinal ganglion cell types, many of which are maximally sensitive (or 'tuned to') particular features within the visual scene (such as spatial frequency or wavelength).

2.3 (B) RETINAL GANGLION CELLS: RECEPTIVE FIELDS AND FUNCTIONS

Kuffler, (1953) in a study of the responses of cat retinal ganglion cells to light, discovered that they had concentric receptive fields. The effect of a spot of light depended upon whether the light fell in a small circular area in the centre of the field, or in a ring shaped area surrounding the centre. Some of the retinal ganglion cells responded with a burst of impulses to either the onset of a spot of light in the centre of the field, or to the offset of a spot of light in the surround. These were called 'centre-on response' cells. Other cells showed the converse, centre-off responses, i.e. offset of a spot of light in the

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[32] The rods and cones encode the visual image in different intensity ranges. Rods detect a narrow range of low light intensities and consequently are specialised for night time vision. Cones detect a wide range of light intensities and are therefore specialised for daytime vision. The specialisation of the rods and cones is possible because their response to light is not a simple function of absolute intensity, but of changes in light intensity (resulting from the process of adaptation), this ensures that they have maximum sensitivity to changes around whatever the current background light level may be, with cones adapting to higher levels of illumination than the rods (see Forrester et al., 1996 for a review).

[33] (the activity of which is modulated by the amacrine neurones of the retina, Forrester, Dick, McMennamin and Lee, 1996).

[34] The region of the retina in which stimulation affects the ganglion cell's firing rate.

centre of the field or onset in the surround, caused a burst of impulses. Because light falling in the two regions of the receptive field had opposite effects the centre and surround were characterised as being antagonistic to one another. When the intensity of light falling on the 'on' region increased or decreased, the strength of the cell's response changed in the same direction. An increase or decrease in light intensity in the 'off' region caused the response to change in the opposite direction (see Bruce et al., 1997 for a review).

Subsequent studies by de Monasterrio and Gouras, (1975) and Dreher et al., (1976) revealed that the majority of monkey retinal cells also had concentric on- or off-centre receptive fields, which tended to fall into two types. One type, the parasol cells, had relatively large cell bodies with radiating dendrites. These cells had large receptive fields, responded transiently to stimulation and had rapidly conducting axons. The second type, the midget cells, had smaller cell bodies with less extensive dendrites. These cells had small receptive fields, responded in a sustained manner to stimulation and had a slow conduction velocity.

The connections of the parasol and midget cells with the photoreceptors were found to result in their ability to abstract different types of information, or features, from the visual scene. For example, as a result of all three types of cone receptor converging (via bipolar, horizontal and amacrine cells) on the receptive field centre and surround of the parasol cells, the parasol cells have spectrally broad band properties. The peak sensitivities of centre and surround are therefore of the same wavelength and consequently little response is produced to monochromatic light filling the receptive field. Strong responses do occur however to a difference in luminance between centre and surround across a broad band of wavelengths.

The midget cells by contrast, receive input from only one or two cone types with different types of cone driving the two parts of the receptive field. The peak sensitivities of the centre and surround regions are at different wavelengths and they respond therefore to both the wavelength of light in their field and differences in light intensity (or luminance) between centre and surround. The midget cells therefore process information about wavelength independently of its intensity. Because of their different responses to colour stimuli, the parasol and midget cell types have been called broad band and colour opponent respectively but are now more commonly respectively known as M (magnocellular) and P (parvocellular) cells.

In addition to the differences in colour processing Kaplan et al., (1990) have demonstrated numerous other differences in the sensitivities of the M and P cells to various aspects of the visual scene. As with colour, the sensitivity of the cells to these other scene attributes is the result of different patterns of photoreceptor connections and the spatial and temporal dynamics of their receptive fields. Table 2.1,

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[35] Such as the 'primitives' of opponent colour and change in luminance.

illustrates some of these properties. (The functional properties of the P and M systems will be discussed further in section 2.9 describing the lateral geniculate nucleus).

TABLE 2.1: The properties of parvocellular (P) cells and magnocellular (M) cells

P CELLS	M CELLS
Give a tonic (or sustained) response to a stimulus, continuing to fire impulses while it is present in the receptive field.	Show a phasic (or transient) response that fades quickly if the stimulus does not change.
Have thin axons with slow conduction rates, i.e. a conduction velocity of 6m/s.	Have thick axons with fast conduction rates, i.e., a conduction velocity of 15 m/s.
Small receptive field centres.	Large receptive field centres.
Low contrast sensitivity, therefore good for seeing high contrast stimuli.	High contrast sensitivity, therefore good for seeing low contrast stimuli
Constitute the majority of retinal neurones, about 80%, with the greatest density in the fovea.	Not found in the foveal region of the retina; their number increases with the distance outwards into the peripheral retina from the fovea.
Slow responding and integrates stimulus energy over long time intervals.	Respond quickly and briefly to changes in visual stimuli.
Well suited for the detection and discrimination of fine detail and are therefore good for the perception of form and very slow movement.	Respond particularly well to small differences in light levels, flickering stimuli and rapidly moving stimuli.
Maximally sensitive to low temporal frequencies and therefore have low temporal resolution and are therefore relatively insensitive to rapidly changing stimuli.	Have high temporal resolution and therefore sensitive to rapidly changing stimuli.

The output from the ganglion cells thus enables the retina to actively signal the presence of certain features in the visual scene. These features include intensity, pattern, boundaries, edges, colour, movement and contours[36]. This information is then encoded and transmitted to other areas of the brain for further analysis.

[36] The rate at which a concentric field in the retina fires impulses signals the degree of contrast between the centre and surround regions of the field, i.e. spatial changes in light intensity. This is achieved by the interaction between antagonistic regions in the receptive field known as lateral inhibition (the reduction in activity in one neuron by activity in a neighbouring neuron; a method of sharpening the contrast at borders) and serves to enhance the responses of the nervous system to change. The combined efforts of these ganglion cells send a map of the visual field to the brain that highlights areas where there are changes in the level of illumination such as the edges of objects (Bruce et al., 1997). The perception of intensity is therefore principally encoded in the retina by the pattern and level of activity of the retinal ganglion cells.

The retinal ganglion axons, which are already differentiated and partially segregated with respect to the kinds of information they convey, exit the eye via the optic nerve. The information is then conveyed to subcortical and cortical areas of the brain.

2.4 THE OPTIC NERVE AND TRACTS

The retinal ganglia converge on to the optic disc and form the optic nerve. The axons from each eye project from here through the optic canal to merge at the optic chiasm where they form the optic tract. Fibres from the nasal half of each retina decussate within the optic chiasm and thus project to the contralateral side of the optic tract and brain. Fibres from the temporal half of each retina project to the ipsilateral optic tract. This configuration is such that the axons from the temporal half of the left retina and the nasal half of the right retina project to the left optic tract, thus bringing information from the right visual field to the left side of the brain and vice versa. Images of the same object formed on the right and left retinas can therefore be processed together in the same part of the brain.

The optic tracts project round the cerebral peduncle of the rostral midbrain. Each divides into a large lateral root which terminates posteriorly in the lateral geniculate body and a smaller medial root, which projects to parts of the brainstem (particularly the superior colliculus). Projections also extend to the pre-tectal area (serving the pupillary light reflex[37]), the reticular formation (concerned with arousal) and the suprachiasmatic nucleus of the hypothalamus (concerned with photoperiod regulation), Van Essen and DeYoe, (1995).

The two major pathways emanating from the optic tracts are the retinogeniculate and retinotectal pathways respectively. They are represented in figure 2.2, together with some of the other pathways and their proposed function.

2.5 THE RETINOTECTAL PATHWAY

The retinotectal pathway forms the phylogenetically older and smaller of the two pathways. It commences when a number of fibres from the optic tract branch off and project to the superior colliculus (SC) in the brainstem. The majority of the cells whose axons make up this pathway appear to be of the M-type and form a retinotopic arrangement in the SC.

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[37] (and a number of other reactions to visual stimuli, such as optokinetic nystagmus, the visual control of posture and certain aspects of locomotion)

The SC receives afferents not only from the retina, but also from the spinal cord and inferior colliculus. The SC also receives back projections from the occipital, temporal, parietal and frontal cortices (Schiller, 1996). These back projections are also primarily of the M-type. The SC projects to the pre-motor and motor nuclei in the brainstem and spinal cord[38] which control reflex movements of the head, neck and eyes in response to visual stimuli (Waxman and de Groot, 1995). The SC also projects to the pulvinar and lateral posterior nuclei of the thalamus from where there are projections to the extrastriate visual areas such as V2, but none, it appears, to the striate cortex, (Coren, Ward and Enns, 1994).

The SC pathway contributes to eye and head movements in response to visual stimuli (even when a person is not conscious of the stimuli), the control of saccadic eye movements, the detection and location of visual stimuli and some aspects of motion processing[39]. The SC contains many cells that fire only when stimuli appear in specific locations in the visual field and appears to co-ordinate the localisation of objects in space and the guidance of eye movements (Schiller, 1996). The non-conscious processing of visual stimuli thought to occur in the retinotectal pathway is believed by many to result in the phenomenon of blindsight[40].

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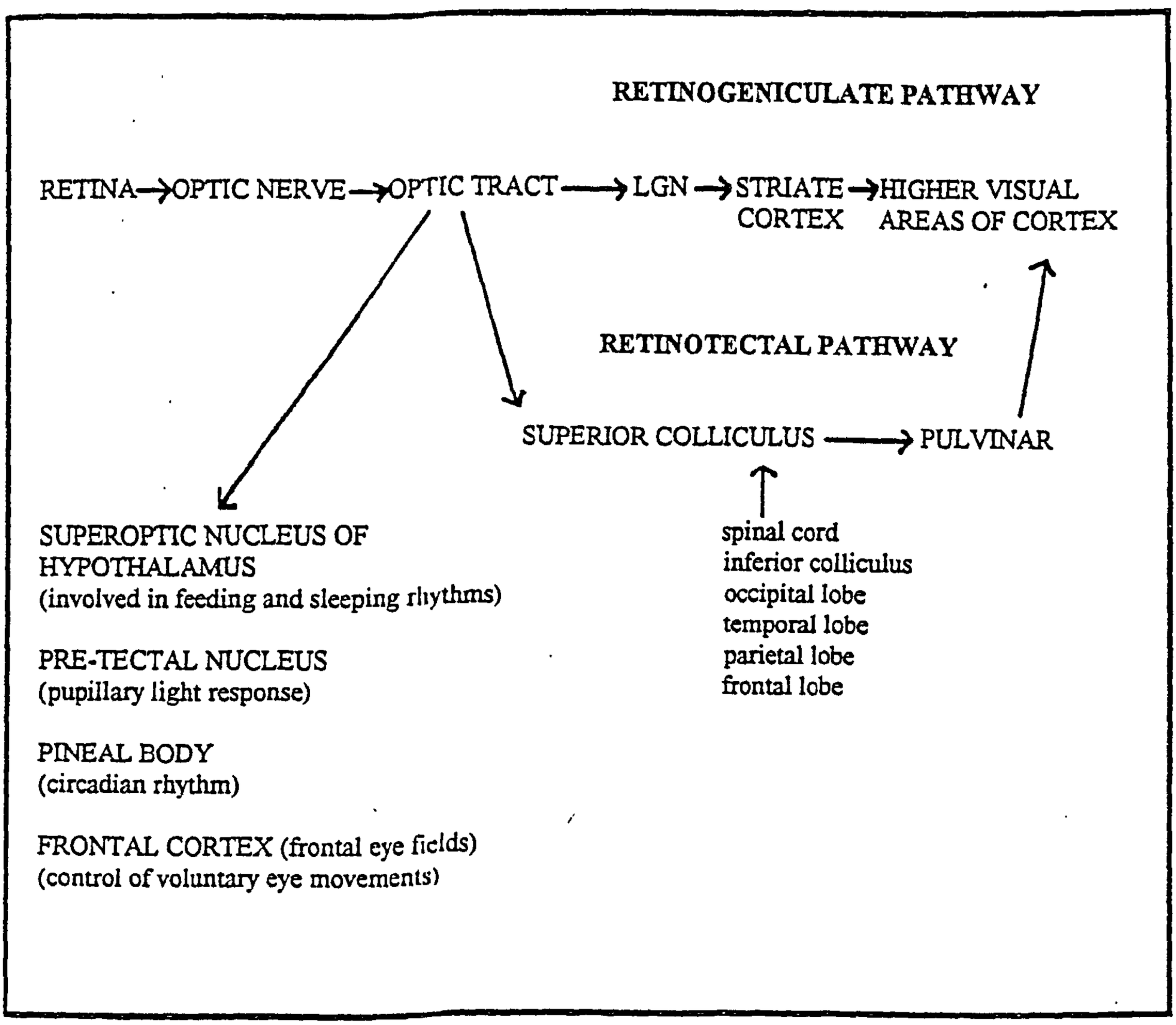
[38] (via the tectospinal tracts)

[39] In particular, the cells here have a receptive field organisation with a preference for the motion detection involved in rapid 'reflex' locking-on movement that occurs in the initiation of tracking a moving target or in automatic scanning during reading.

[40] Lesions of the striate cortex can result in scotomas or total cortical blindness where the individual fails to acknowledge seeing stimuli in the affected parts of the visual field. However, some individuals with such damage retain the potential for the processing of stimuli presented in the scotoma and are said to exhibit blindsight (Poppel, Held and Frost, 1973). Early studies, by Weiskrantz, Warrington, Sanders and Marshall, (1974); Perenin and Jeannerod, (1978) and Zihl, (1980), resulted in the general conclusion that those individuals who can use visual information for behaviour, such as reaching, without any conscious visual experience, were utilising visual information transmitted by pathways other than the retinogeniculate pathway; the retinotectal pathway being considered the most likely.

However, Campion, Latto and Smith, (1983) claimed that blindsight could be attributed instead, to either the fact that light from the target might have spread, (by scattering) to portions of the retina unrelated to the scotoma or that there may be spared tissue within the cortical region mediating visual processing of the area of the field covered by the scotoma. Celesia et al., (1982, 1991) have shown that in individuals with bilateral lesions of the occipital cortex, residual vision, if present, can be attributed to activation of a remnant of spared striate cortex. In addition, positron emission tomography (PET) studies have failed to demonstrate the activation of a subcortical second system in such damage (Celesia and De Marco Jr, 1994). The debate continues, but it does highlight uncertainty about the function of the retinotectal pathway in vision.

Figure 2.2: Projections from the retina to other parts of the brain.



2.6 THE RETINOGENICULATE PATHWAY (THE PRIMARY VISUAL PATHWAY)

The primary visual pathway, projects from the axons of the optic nerve to the dorsal part of the lateral geniculate nucleus (LGN) of the thalamus. The retinogeniculate pathway contains both M- and P-type neurones and appears to be subdivided in terms of both function and areas of projection.

2.6 (A) THE LATERAL GENICULATE NUCLEUS

There are six layers of the LGN, three layers receive input from one eye and three receive input from the other. Each layer maps the contralateral visual field in a retinotopic manner. The anatomical distinction between the two retinal channels of M and P cells found in the retina is preserved at the LGN. The P ganglion cells project to the four parvocellular layers and the M ganglion cells project to the two magnocellular layers (Dreher et al., 1976; Levanthal et al., 1981). The receptive field and response property characterisation of the M and P ganglion cells also appears to be preserved at the level of the LGN (Derrington and Lennie, 1984; Milner and Goodale, 1997).

LGN cells only appear to respond to visual stimuli occurring within their receptive fields; providing information therefore about the location of particular visual features or objects in space. Like those in the retina, LGN neurones have circular-surround receptive fields. The surround of an LGN receptive field however, exerts a stronger inhibitory effect on its centre than does the surround of a retinal ganglion cell. Lateral geniculate nucleus cells therefore amplify and accentuate differences in illumination between neighbouring retinal regions to a greater extent than retinal cells. This makes LGN cells particularly important for registering the presence of edges.

Livingstone and Hubel, (1988) argued that the M and P cells of the LGN formed the first stages in a two-way division of visual information processing that continued throughout the visual system. They proposed that the M cells represented the first stage of a system responsible for extracting features associated with movement, whereas the P cells performed the first steps in extracting features associated with colour. Animal lesion studies of the M and P neurones of the LGN have been used in an attempt to gain further information about the specific visual information processing capacities of these neurones. Monkeys have been tested on a wide range of visual tasks aimed to determine what aspects of visual feature extraction are impaired after selective lesions to the M or P layers.

For example, Merigan et al., (1993) found that P lesions resulted in deficits of colour discrimination and moderate deficits in form and depth discrimination (especially at low temporal and high spatial frequencies). Kurylo et al., (1994) found selective deficits of flicker and motion with M lesions. However, although Schiller, Logothetis and Charles, (1990) also found that monkeys with a lesion of the P layers had clear deficits in colour, texture, fine shape and pattern discrimination processing, they

found that M lesions affected only the ability to detect motion in a complex display and to discriminate a rapidly flickering stimulus from a steady one. That M lesions did not abolish the perception of motion altogether, but reduced the visibility of moving stimuli, was also found by Merigan, Byrne and Maunsell, 1991.

It is now clear that the most basic visual features such as brightness, texture, pattern, shape, motion, flicker and depth can be processed by both systems. The main difference appears to be that the P system can process information up to higher spatial frequencies, whereas the M system can do so up to higher temporal frequencies (Schiller and Logothetis, 1990; Schiller, Logothetis and Charles, 1990; Merigan et al., 1993).These two systems therefore appear to extend the range of visual information processing, beyond that able to be handled by either type alone, with the P system extending it in the spatial and wavelength domains and the M system extending it in the temporal domain (Schiller and Logothetis, 1990).

So although some support has been obtained for the 'P' & 'M' functional dichotomy proposed by Livingstone and Hubel (1988) the results in general tend to indicate complementary rather than dichotomous processing.

2.6 (B) LATERAL GENICULATE NUCLEUS AND THE KONIOCELLUAR STREAM

Koniocellular (K) cells are also present in the LGN. They are small cells that lie between the P and M layers and are as numerous as M cells (Benson et al., 1991). These K cells have direct projections to regions of the striate cortex and receive selective inputs from the superior colliculus as well as from small diameter axons presumed to arise from the retina (Lachica et al.,1992). It is not yet certain what role the K cells play in visual processing (Casagrande and Lachica, 1992; Van Essen and De Yoe, 1995), but the results of work carried out by Troscianko, Davidoff, Humphreys, Landis, Fähle, Greenlee, Brügger and Phillips, (1996) on a patient with cerebral achromatopsia[41], indicated that chromatic discrimination need not be mediated solely by the P system[42] but may be mediated by a further neural sub-system, possibly the K system.

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[41] (who lacked conscious colour perception but could still make use of colour information)
[42] (which is thought to subserve conscious colour perception)

2.6 (C) FEEDBACK CONNECTIONS AND THE LATERAL GENICULATE NUCLEUS

In addition to the projections to the LGN from the retina and subcortical structures (such as the reticular formation and the oculomotor centres) there are feedback projections to the LGN from the striate cortex and extrastriate areas such as V2. Although their exact function is uncertain, feedback projections may influence the processing of information from the retina to the cortex (perhaps controlling the flow of information, Sillito, Jones, Gerstein and West, 1994). Sillito et al., suggested that the feedback loop between the striate cortex and the LGN operates to boost the activity of those LGN cells that drive a common set of striate cortex cells, in turn strengthening the response in the striate cortex. The LGN does not therefore appear to act as a simple relay between the retina and cortex.

From the LGN, the retinogeniculate pathway projects to the striate cortex (the primary visual cortex), an area of the occipital cortex.

2.7 THE STRIATE CORTEX (V1)

The functional organisation of the striate cortex further facilitates the extraction and processing of the basic features of which the visual scene is composed. The striate cortex also channels the information about specific features to different visual processing areas for further, usually higher-level, processing. The visual scene was found to be retinotopically[43] mapped onto the striate cortex, with the left and the right halves of the visual field mapped onto the right and left cortices respectively. The area devoted to the central part of the visual field was found to be proportionally greater than that devoted to the periphery[44].

The functional organisation of the striate cortex was initially determined from recordings from single cells in the striate cortex of cats (Hubel and Wiesel, 1959, 1962) and in monkeys (Hubel and Wiesel, 1968). The receptive field configurations of striate neurons were found, like those in the retina, to be primarily sensitive to particular features of the visual scene, such as spatial frequency and wavelength. In general, however, the receptive fields of striate neurons were found to be more complex in both structure and function than those in the retina and LGN.

For example, the receptive fields of many striate neurons were found to be in the form of an antagonistic arrangement of elongated excitatory and inhibitory areas lying adjacent and parallel to each other. A different arrangement therefore than the concentric arrangements of receptive fields found in the retina and LGN. As a consequence of their receptive field configuration, striate neurones have a distinct property which is absent in the retina and LGN: they respond most to a particular orientation of

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[43] Retinotopic organization continues beyond V1 to V2 and V3 (Engel, Glovel and Wandell, 1997).

a bar, edge or grating. Hubel and Wiesel, (1968) suggested that such cells were therefore specialised for the processing of orientation-related information.

The receptive fields of many striate neurons were also found (unlike those in the retina and LGN), to exhibit dual colour opponency in which different regions of the receptive field show opposite colour-opponent responses (Thorell, De Valois and Albrecht, 1984; T'so and Gilbert, 1988). An additional property of many of these cells was their responsiveness to binocular input (not seen in cells of the retina or LGN), see Bruce et al., (1997) for a review.

2.8 STRIATE CORTEX ORGANISATION

The striate cortex has six principle layers, the outermost being labelled as one. The axons from the LGN project to layer 4 of the striate cortex: cells in this layer respond to a stimulus presented in one eye only, just as the cells in the LGN do. The P neurones project to neurones in a sub-layer of layer 4, 4C beta. The M neurones project to sub-layer 4C alpha. The outputs from these sublayers of 4C in turn project to other layers in the striate cortex. Cells in 4C alpha project to layer 4B and cells in 4C beta project to layers 2 and 3, which then project to extrastriate regions. Layer 5 of the striate cortex sends a major output to the SC and layer 6 sends a substantial output back to the LGN[45]. The different patterns of connectivity within the layers of the striate cortex appear to facilitate the segregation and subsequent concurrent processing of the different features comprising the visual scene.

The striate cortex is highly organised and modular in nature. The neurons are organised in the form of a highly complex system of distinct modules or columns, each concerned with visual analysis within a specific portion of the visual field. Alternating columns of cells show a preference for responding to stimuli coming from one eye or the other. These so-called 'ocular dominance columns' can be further

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[44] (mainly due to the greater density of retinal ganglion cells in the central retina).

[45] Wong-Riley (1979), had earlier revealed the existence of a regular array of dark blobs of tissue rich in cytochrome oxidase (CO) predominant in layers 2 and 3 (where the P cells project to) but absent in layer 4. Livingstone and Hubel (1984) and Hubel and Livingstone (1987) showed that both the blob and interblob regions receive inputs primarily from the P system (via 4C beta). The cells in the blob regions appeared to be predominantly colour selective in a double opponent fashion, having little or no orientation selectivity, binocularity or selectivity for movement direction; responding best to relatively low spatial frequencies. The interblob regions had relatively little colour sensitivity, showed a preference for high spatial frequencies and selectivity for stimulus orientation and often for binocular disparity (Lennie et al., 1990, however found that some of the interblob cells have selectivity for both orientation and colour). Layer 4B, (which receiveS projections primarily from the M layers of the LGN) was found to contain a high proportion of cells selective for the direction of stimulus motion. Cells in 4B were found to have a high incidence of orientation selectivity and sensitivity to binocular disparity, but rarely showed colour selectivity. Such findings were generally interpreted as indicating that different neurones in the striate cortex not only processed different features of the visual scene, but utilised different pathways of connections to do so.

subdivided into regularly arranged columns of orientation-selective neurones. These neurones respond to an edge or bar in their receptive fields only when it is held at a particular orientation. All the neurones in one column respond to one orientation; neurones in the adjacent column respond to an orientation a few degrees off from the first and so-on until all orientations are covered. A region of cortex containing all 360 degrees of orientation specificity (including a region responsive to both left and right eye), forms a unit called a hypercolumn (see Coren et al., 1994, for a review). Interwoven with the orientation-selective neurones are columns of neurons with other functional properties, such as spatial frequency, wavelength, orientation and motion selectivity.

This modular arrangement enables the entire visual scene to be processed in parallel thus determining the features present in each area of the retina at the same time.

The striate cortex was initially characterised by many, (including Barlow, 1972) as creating a representation of the visual world in terms of features, with the neurones of the striate cortex acting as feature detectors, each signalling the presence of a specific feature of visual information. This proposal is now known to be an oversimplification. DeValois et al., (1982); DeValois and DeValois, (1990) and Van Essen, Anderson and Felleman, (1992) proposed that neurones acted instead as relatively broadly tuned filters for multiple dimensions of the information contained within the visual image, such as spatial frequency, colour and motion information. According to DeValois and colleagues, the neurones perform a computation similar to the mathematical technique of Fourier analysis in order to extract this information. The firing rate of the neurone was interpreted as providing a measure of the features to which the neurone is most sensitive, with the presence of particular features inferred only from comparisons across populations of cells.

So although the striate cortex neurones have distinct maximal response properties to particular features of the visual scene (Levitt, Lund and Yoshioka 1996), they act as multidimensional filters thereby exhibiting great functional diversity. A given cell in the striate cortex will respond to motion when present in the visual scene but will, in the absence of motion, also respond to line segments of particular orientation, and to a range of colours (when the cones are active) and to achromatic stimuli (under dark adapted conditions[46]). Zipser, Lee, Lamme and Achiller (1994) also found that a neurone's response may be modulated by a variety of stimulus conditions in other neurones (see Schiller, 1996, for a further review of this research).

The striate cortex is not therefore an area specialised for the processing of any one particular aspect of visual information. The striate cortex appears instead to signal the presence of certain visual features

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[46] Malpeli, Achiller and Colby, (1981) also found that although some cells are driven selectively by the P or M cells, there are numerous cells which receive a convergent input from these two systems, thus indicating their potential range of functions.

and after the initial, relatively low level processing of these features, to channel the information to other areas for further, more specific and higher level processing.

[Of particular importance to the present study is that the visual processing associated with the striate cortex occurs automatically, i.e., independently of the need for attention. This important factor will be discussed in detail in a further section].

2.9 EXTRASTRIATE REGIONS (V2, V3, V4 AND V5)

From the striate cortex, the resultant major projection is to the extrastriate areas. The extrastriate areas appear to be both anatomically and functionally placed between the relatively low level processing region of the striate cortex and the high level processing regions of the temporal and parietal association cortices. Each extrastriate region appears to be specialised to process a particular type, or narrower range of visual information compared to the striate cortex. The extrastriate regions appear therefore to have greater functional specialisation than that found in the striate cortex (Bressler, 1996).

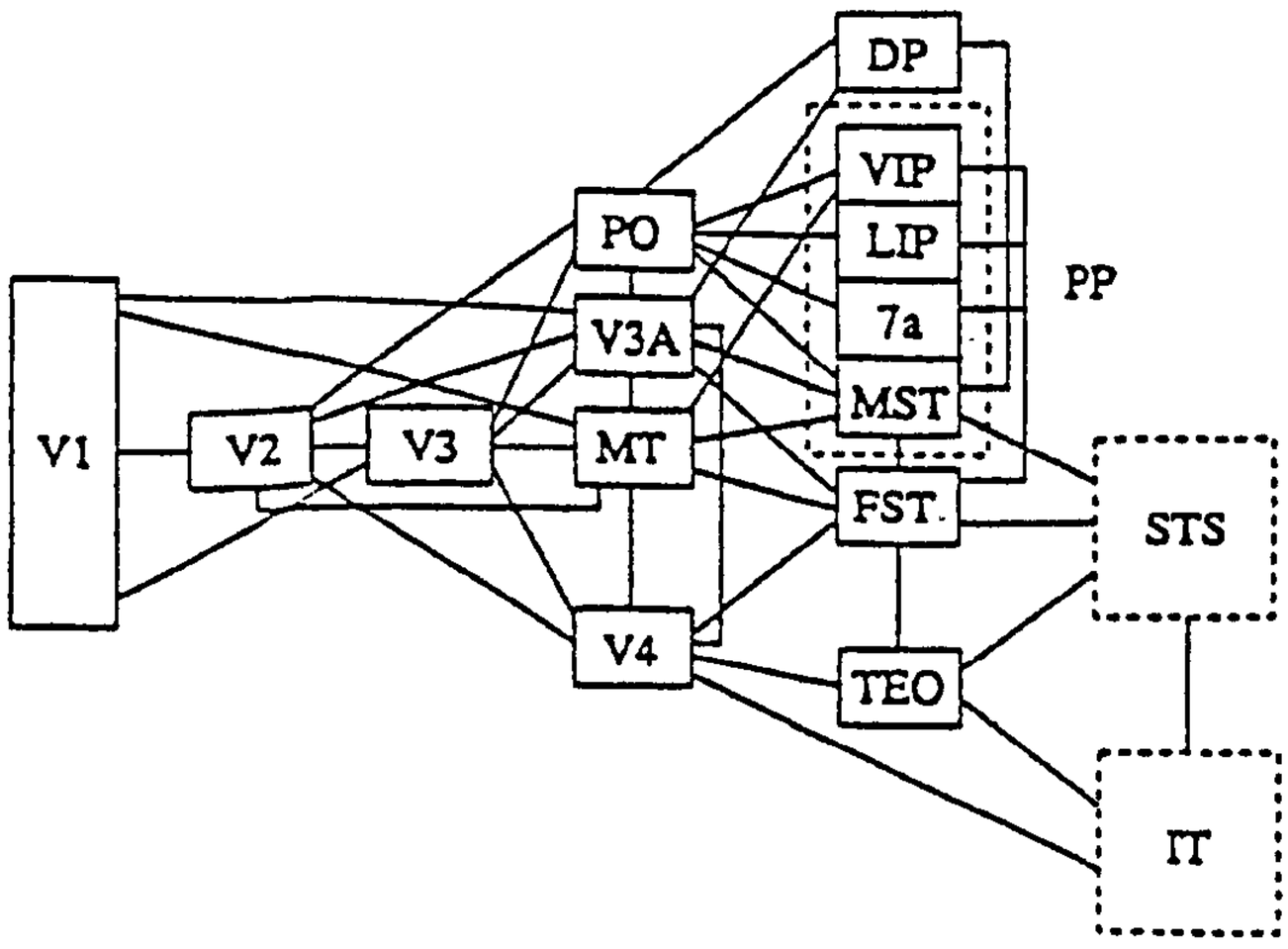
Evidence that the extrastriate visual areas tend to be specialised for the processing of a narrower range of visual information has been obtained primarily from single cell electrophysiological studies. The results of such studies have tended to indicate that the neurones of individual extrastriate regions are largely those which are selective for fewer features of visual information compared to those of the striate cortex. The response characteristics of extrastriate areas are therefore less multifunctional than those of the striate cortex (Bressler, 1996).

The selectivity for complex stimuli found in the extrastriate areas but absent in the striate cortex provided evidence that more complex processing occurred in the extrastriate areas compared to the striate cortex, thus pointing to the existence of some hierarchical processing of information (Bressler, 1996).

The extrastriate cortices were traditionally organised into a hierarchical scheme in which they were placed at different levels according to their distance from the striate cortex (Maunsell and Newsome, 1987). Although this organisation will be followed in the following description of these areas, it is now clear that there is less hierarchical organisation than originally thought. Figure 1.3 shows some of these connections.

Figure 2.3

Schematic Representation of Information passing from Striate cortex to Extrastriate and Visual Association areas



KEY

PO parietal occipital areas	MT middle temporal area (V5)
DP dorsal prestriate area	VIP ventral intraparietal sulcus area
7a parietal area 7a	LIP lateral intraparietal sulcus area
MST medial superior temporal area	FST fundus of the superior temporal sulcus
PP posterior parietal complex	STS anterior complex of superior temporal sulcus
IT inferotemporal complex	

From Distler et al., (1993) and Milner and Goodale, (1997).

(The main target area for projections from the striate cortex is the adjacent area of the occipital cortex, V2).

2.10 EXTRASTRIATE AREA V2

Extrastriate area V2 of the occipital cortex, surrounds and receives its primary excitatory drive from the striate cortex. Thalamic afferents from the LGN also project to V2. Feedforward projections from V2 pass to several other visual areas including V3 and its subdivisions, V4, V5, the parietal and temporal cortices and the frontal eye fields (Merigan et al., 1993).

Electrophysiological single unit studies (Livingstone and Hubel, 1984) have revealed that many neurones in V2 have multidimensional visual information filtering properties similar to those found in the striate cortex. Consequently, like the neurones in the striate cortex, the neurons of V2 do not seem to detect specific stimuli, but rather respond in a tuned fashion, along several different stimulus dimensions. There are however some structural[47] and functional differences between the striate cortex and V2.

Like many of the cells in layer 4B of the striate cortex, which receives inputs primarily from the M pathway, the majority of the cells in the thick stripes of V2 have been found to be tuned for retinal disparity, motion direction and orientation (De Yoe and Van Essen, 1995). The thick stripe neurones would appear therefore to be particularly adapted for extracting stereoscopic information about depth and motion. Cells in the thin stripes, like the cells in the striate cortex blobs show no evidence of orientation or direction selectivity but over half of them are colour coded. Like the colour-sensitive cells in the blobs, these cells are of the double-opponent type. The thin stripes, like the blobs in the striate cortex, contain cells that are particularly well suited to the processing of colour information. The remainder of the cells in the thin stripes are rather broadly tuned for wavelength.

Cells in the pale stripes like their counterparts in the interblob regions of V1 are orientation selective. However, unlike the majority of interblob cells, those in the pale stripes of V2 are also 'end-stopped', responding best therefore to short rather than long edges or lines. Hubel and Livingstone, (1987) found none of the pale stripe cells to be explicitly tuned for colour (see however, Merigan et al., 1993). The interblob pale stripe channel appears instead to encode information about the shape or configuration of visual stimuli.

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[47] In particular, histological staining in V2 has revealed the existence of histologically distinct subdivisions similar to those found in the striate cortex, but rather than being arranged in terms of blobs and interblobs (see footnote 45) take the form of three types of region; alternating thick and thin stripes separated by pale interstripes. The stripe regions of V2 receive specific connections from the blob and interblob regions of the striate cortex. The blobs project to the thin stripes, the interblobs project to the pale interstripes and layer 4B of the striate cortex projects to the thick stripes.

An organisation particularly prominent in V2 is that associated with disparity. Many of the cells show strong responses to retinal disparity, a specialisation for stereoscopic vision. Directional cells are also more numerous in V2 than the striate cortex.

Neurones from V2 project to numerous extrastriate areas, such as V3, V4 and V5.

2.11 EXTRASTRIATE AREA V3

Area V3 a further sub-division of the occipital cortex, receives input directly from the striate cortex and also via the thick stripes of V2. Single unit electrophysiological studies have indicated that area V3 contains predominantly orientation-selective cells, with response depending mostly on an object's speed and direction of movement. As about half of the cells in V3 are directionally sensitive, V3 is more specialised to abstract directional information than V2 and the striate cortex. V3 has better temporal acuity than V2 (Van Essen and De Yoe, 1995) and appears to be specialised for the processing of dynamic form while appearing to be relatively indifferent to wavelength (Zeki, 1978a, 1978b). From V3, neurones project to visual areas in the parietal, occipital and temporal cortices, and the frontal eye fields (Milner and Goodale 1997).

2.12 EXTRASTRIATE AREA V4

Area V4 in the ventro-medial occipital area (in the lingual gyrus, Zeki et al., 1991) receives a major projection from the thin stripes and pale stripes of V2. This route from the blob and interblob zones of V1 through the thin and pale stripes of V2 to V4 suggests that wavelength selectivity as well as orientation selectivity might be transmitted to V4. The properties of the neurones in V4 suggest they exhibit an increased specialisation for colour processing compared to that of the striate cortex. For example, Zeki, (1983) found that some V4 cells exhibited colour constancy[48] whereas the responses of cells in the striate cortex provided no evidence of colour constancy, but were selective for wavelength alone. Although V4 is primarily characterised as being 'specialised' for colour processing, information about shape, depth and motion is also processed (Ferrera, Nealey and Maunsell, 1994, Cheng et al., 1994; Desimone et al., 1985; Schein and Desimone 1990).

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[48] Surfaces and objects retain their colour in spite of wide ranging changes in the wavelength and energy composition of the light reflected from them. It appears that the wavelength-selective cells of V1 are concerned with the component wavelengths reflected from a surface, whereas the cells in V4 are concerned with the colour of a surface (see Zeki, 1992, 1993; Land, 1983; see Tovee, 1996 for a review). This finding is consistent with lesion studies performed with laboratory primates which have indicated that the removal or damage of V4 leaves them able to discriminate wavelength but impaired in terms of colour constancy (Wild, Butler, Carden and Kulikowski, 1985).

2.13 EXTRASTRIATE AREA V5

Area V5 (positioned just posterior to the meeting point of the ascending limb of the inferior temporal sulcus and the lateral occipital sulcus, Watson et al, 1993) receives projections from V1, V2, V3 and V4, the temporal and parietal lobes and from the frontal eye fields. It has also been demonstrated that there is a direct input to V5 from the lateral geniculate nucleus thus bypassing the striate cortex (Beckers and Zeki, 1995; ffytche, Guy and Zeki, 1995). This was an important finding as it indicated that specialised areas of the visual cortex were able to contribute directly to visual perception without the necessity of pre-or post processing by the striate cortex (Beckers and Zeki, 1995; ffytche et al., 1995). Such a finding indicates therefore that visual processing is not purely hierarchical in nature.

Many neurones in V5 are both motion and direction sensitive and in comparison to neurones in the striate cortex[49], are responsive to more complex properties of motion than just its detection. In V5, the firing pattern of the neurones reflects the speed and direction (i.e., the velocity) of an object as a whole. V5 is also selective for illusory motion (see Albright, 1993; Merigan et al., 1993; McCarthy, Spicer, Adrignolo, Luby, Gore and Allison, 1995; Tootell et al., 1995). Area V5, appears therefore to process more complex aspects of motion and is a more functionally homogenous area than the striate cortex.

Neurons project from V5 to the adjacent cortical area V5a, where many neurones, in addition to displaying motion direction selectivity, are tuned to more complex motion patterns such as expansion, rotation and contraction (Tanaka et al., 1986; Duffy and Wurtz, 1991; Geesaman and Anderson, 1996; Lagae et al., 1994).

2.14 EXTRASTRIATE AREAS AND THE DIVISION OF LABOUR

The extrastriate visual areas provide further evidence of the multi-area, multi-distributed nature of visual processing. Although still capable of processing several types of visual information, each of the extrastriate areas appears to be specialised for extracting a certain feature of the visual scene, such as motion (V5) or colour (V4) but does so at a higher level of complexity than that found in the striate cortex. This distribution or division of labour of visual information processing found throughout the striate cortex and the extrastriate regions is thought to enable multiple processes and computations to operate concurrently thus producing rapid and efficient visual processing (Zeki, 1990).

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[49] In the striate cortex the neurones are sensitive to particular directions of motion (Maunsell and Newsome, 1987), with the response of single neurones ambiguous with respect to the direction of motion of the whole object

2.15 CORTICAL VISUAL PATHWAYS

Drawing on evidence from studies on the effects of brain lesions on visual function, Ungerleider and Mishkin, (1982) suggested that the extrastriate areas could be segregated in terms of belonging to one of two independent processing streams emanating from V2. One pathway projecting to the parietal lobe, was described as being responsible for extracting high level information (from the pattern of activity of striate cortex cells), about the spatial layout of the environment and motion. A second pathway projecting to the temporal lobe was described as extracting high level information about the form, colour and identity of objects. These pathways were termed the dorsal (where) and ventral (what) pathways respectively (Maunsell, 1987; De Yoe and Van Essen, 1988; Livingstone and Hubel, 1988; Desimone, Albright, Gross and Bruce, 1984).

2.16 THE DORSAL PATHWAY PROJECTIONS

According to Ungerleider and Mishkin, (1982) and Seeck et al., (1995), the dorsal pathway is characterised as projecting from V2 to V3 to V3a to V5 and then via the medial superior temporal area (MST) to area 7a in the parietal lobe.

2.17 THE VENTRAL PATHWAY PROJECTIONS

According to Ungerleider and Mishkin, 1982; Desimone and Ungerleider, 1989; Seeck et al., 1995, the ventral pathway projects from V2 to V4 then from here to the posterior and anterior inferotemporal areas of the temporal lobe and the mediotemporal limbic structures (such as the hippocampus and amygdala[50]) and on to the ventrolateral frontal cortex .

Evidence supporting Ungerleider and Mishkin's, (1982) separate pathway theory has been found from the results of PET studies. For example, Haxby et al., (1991) obtained PET scans while people performed either a spatial (dorsal pathway task) or a face matching task (ventral pathway task). In both cases, activity in the occipital cortex increased relative to a control condition and activity increased in the temporal lobe during the face matching task, but in the parietal lobe during the spatial task. Similar dichotomous results have been obtained by Tootell et al., (1996) and Ungerleider and Haxby, (1994) who also identified the temporal regions for object identification and the posterior parietal region for spatial or location tasks. Further evidence for the segregation of two pathways involving different extrastriate

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[50] (the amygdala plays a critical role in associating complex visual information with emotional states and social scenes)

areas can be found by tracing neural connections back from the posterior parietal and the inferior temporal cortex (Young, 1992).

2.18 THE RELATIONSHIP BETWEEN THE M AND P SYSTEM AND THE DORSAL AND VENTRAL PATHWAYS

Livingstone and Hubel, (1988) argued that the dorsal and ventral pathways were direct continuations of the subcortical M and P pathways respectively. The P pathway was interpreted as functioning as a 'what' system, which develops a representation of an object and the M pathway was interpreted as functioning as a 'where' system. Livingstone and Hubel based their hypothesis in part, upon the apparent correlation between the results of human psychophysical data and the electrophysiological characteristics of the P and M pathways (Milner and Goodale, 1997). It is now apparent however, that such a simple relationship does not exist.

2.19 PROBLEMS WITH THE RELATIONSHIP BETWEEN P AND M AND VENTRAL AND DORSAL PATHWAYS.

Considerable evidence now exists that the M and P pathways are heavily intermingled and therefore do not form two functionally distinct inputs to the cortex. For example, the response characteristics of retinal and LGN cells in the two pathways show a large overlap in the range of effective stimuli in the spatial and temporal domains, even though the mean responses are rather different (Merigan et al., 1993). There is also physiological evidence for an M input to the blobs in the striate cortex (Livingstone and Hubel, 1984; Lachica et al., 1992).

Ferrera, Nealey and Maunsell, (1994) also showed that blocking P or M layers of the LGN was equally effective in reducing activity in V4. This would suggest therefore that input to this area (and thus to the ventral pathway) originates from both the P and M systems. There is also evidence that P as well as M pathways provide input to V5 (Maunsell et al., 1990). While inactivation of the M layers of the LGN reduces the responsivity of almost all cells tested in V5, some cells in this dorsal stream area are also affected by inactivation of the P layers, though the effects are much less substantial (Maunsell et al., 1990).

So contrary to Livingstone and Hubel's, (1988) proposal, the ventral and dorsal streams both appear to receive inputs from the M and P pathways. Although most of the input to the dorsal stream is 'M' in origin, the ventral stream is considerably more mixed with apparently as many inputs from the M as the P system. There does not therefore appear to be strict correspondence between dorsal and ventral and M and P (Felleman and Van Essen, 1991; Young, 1992; Milner and Goodale, 1997).

A great deal of connectivity between these two pathways appears to exist[51], not all of it is feedforward. Numerous feedback projections exist, with many visual areas receiving inputs from both lower and higher levels of brain processing, with higher areas able to modulate the activity of lower order ones (Friston, Ungerleider, Jezzard and Turner, 1995; Bressler, 1996). In addition to the input to these areas that arises from the retinal projections to the LGN, there is a significant contribution from the SC (this input being more evident in the dorsal than in the ventral stream, see Milner and Goodale, 1997 for a review).

2.20 NEW CONCEPTS ON THE TWO PATHWAY HYPOTHESIS.

More recently, Milner and Goodale (1993, 1997) have proposed a significant modification of Ungerleider and Mishkin's original two pathways model. Milner and Goodale considered it unlikely (as the original distinction between the 'what' and 'where' pathways would suggest) that the two pathways evolved to handle different aspects of the stimulus array. According to Milner and Goodale, spatial processing is characteristic of both the dorsal and the ventral visual streams, with visual space coded differently in both streams. According to Milner and Goodale the spatial coding found in the dorsal stream has more to do with the guidance of particular forms of action rather than spatial perception and suggest that spatial perception (such as encoding the spatial layout of the environment) is associated more with the ventral stream[52]. This concept forms a substantial area of research, the discussion of which is beyond the remit of the present study (for a detailed review see Milner and Goodale, 1997)[53].

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[51] The connections appear to be laminar-specific, with contrasting patterns of laminar origin and termination of pathways being used to arrange visual areas into anatomical hierarchies, Elston and Rosa, 1997).

[52] According to Milner and Goodale, the original 'what-where' model could not explain new behavioural evidence about the nature of dorsal stream processing. Milner and Goodales' proposal arose from their observations of a patient who although blind, could shape her hand appropriately when asked to reach for objects. Importantly, her dorsal stream was intact. Other patients with dorsal stream damage, could consciously report seeing objects but could not shape their hand appropriately when reaching. Milner and Goodale therefore proposed that rather than characterising the dorsal stream as a 'where' system, it should be thought of as a set of systems for the 'on-line visual control of action'.

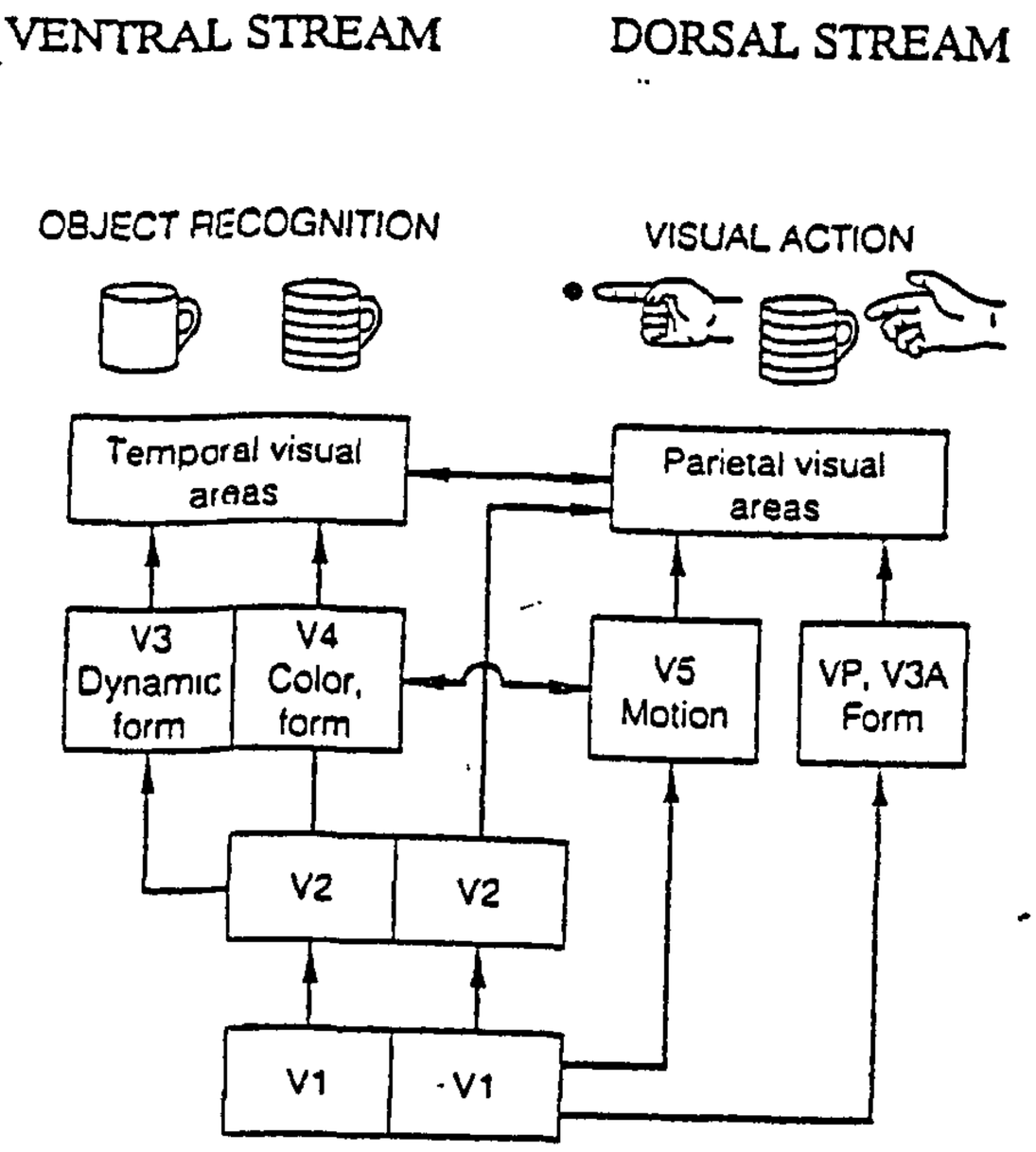
Their argument was based upon several further lines of evidence. For example, a predominant characteristics of the neurones in the posterior parietal regions is that they are active during a combination of visual stimulation and associated behaviour, i.e. being active only when the brain acts on visual information. This according to Milner and Goodale, suggested that these neurones can be characterised as an interface between analysis of the visual world and motor action upon it. They argued therefore that the role of the dorsal stream was more likely to be in sensory-motor co-ordination (i.e. visuomotor transformations underlying visuomotor actions), than in spatial vision.

Milner and Goodale (1993; 1997) suggested that the differences between dorsal and ventral streams can be explained on the basis of the use to which the two streams put visual information together, rather than on the basis of the kind of visual information analysed.

According to Milner and Goodale while it is true that different channels in the visual system are specialised for different kinds of analysis (e.g. M versus P) at some point, these separate inputs are combined and transformed in different ways for different purposes. Consequently both cortical streams

Figure 2.4: The Ventral And Dorsal Streams

(after Milner and Goodale 1993).



process information about the intrinsic properties of objects and their spatial locations, but the transformations they carry out reflect the different purposes for which the two streams have evolved. The transformations carried out in the ventral stream result in the formation of perceptual and cognitive representations which embody the characteristics of objects and their significance; while those carried out in the dorsal stream, mediate the control of goal directed actions.

Suggesting therefore that the division of labour between the ventral and dorsal streams can best be characterised in terms of a distinction between the roles of vision in perception and action respectively; with the ventral pathway primarily concerned with the visual perception of objects, with the dorsal stream mediating the required sensorimotor transformations for visually guided actions directed at those objects (Goodale and Milner 1991; Milner and Goodale 1993). Figure 4 illustrates this distinction.

[53] The proposals put forward by Milner and Goodale may have implications for the conclusions drawn from previous studies of late visual processing which have interpreted the effects of damage to the parietal and temporal lobes in terms of the original visual pathway organisation described by Ungerleider and Mishkin, 1982.

2.21 THE BINDING PROBLEM

The distributed nature of visual processing described in the previous sections begs the question of how the brain integrates this distributed activity (that corresponds to the low level representation of visual features) to form high level conscious and unambiguous perception. This is known as the binding problem. It became clear that there was not a single cortical area that received input from all the other areas and bound or integrated it into a single percept of the visual scene. Consequently several proposals for the solution of this problem were put forward.

For example, Barlow (1972) proposed the 'cardinel cell' hypothesis. Barlow proposed the existence of cells selective for very specific groups of features (via convergence of the outputs situated in lower visual areas). This strategy would however be unrealistically expensive in terms of the number of neurones needed for encoding objects, given the virtually infinite diversity of possible feature combinations (Sejnowski, 1986). An alternative solution to the binding problem employed the 'focus of attention' (Treisman, 1986, 1996). According to this proposal, when the spotlight of attention can be positioned accurately to include a single object, the binding problem may be circumvented. But, positioning the spotlight around a single object is not always possible, especially if the objects are in close proximity or are occluding (Engel et al., 1997).

A further solution to the binding problem was proposed by Von der Malsburg, (1995); Gray et al., (1989) and Gerstner et al., (1996). They suggested that as time constitutes an important variable for neural information processing the synchronisation of neural activity on a millisecond scale may reflect the dynamic coupling of the featural information represented by distributed neurones. Such a mechanism would therefore enable the integration and selection of 'coherent' chunks of perceptual information by 'coincidence-sensitive' neurones in other brain areas (Gerstner et al., 1996).

This temporal binding model predicts that neurones which respond to the various features of a single image component should synchronise their discharges on a fine temporal scale, whereas neurones that respond to different image components should not fire in synchrony. A critical advantage of this coding strategy is that it allows multiple assemblies to become active at the same time without becoming confounded (Von der Malsburg , 1995; Engel et al 1992; Singer and Gray 1995).

Despite these suggestions however, the binding problem is far from solved (for a detailed review of this subject see Engel et al., 1997).

2.22 AUTOMATIC AND ATTENTION-RELATED VISUAL PROCESSING

A dichotomy between automatic and attention-related visual processing is recognised in many accounts of visual processing, for example, Broadbent (1982); Duncan and Humphreys, (1989); Treisman and Sato, (1990); Wolfe, Cave and Franzel, (1989); Wolfe, (1994).

2.22 (A) AUTOMATIC VISUAL PROCESSING.

The spatially parallel extraction and processing of the basic visual features which occurs in the striate cortex is described as being automatic in nature. Such attention-independent processing is triggered simply by the occurrence of appropriate stimuli[54] (Julesz, 1975; Treisman, 1991; Schneider and Shiffrin, 1977; Shiffrin and Schneider, 1977[55]). The entire visual scene undergoes this initial relatively low level processing of visual information.

2.22 (B) ATTENTION-RELATED VISUAL PROCESSING.

The subsequent stages of visual information processing which result in high level representations and perception, require attention for their operation. The limited availability of attention however means that only a limited, selected amount of information from the earlier automatic stage of visual processing can be processed to this higher level at any point in time[56]. The visual system therefore employs a 'mechanism' which selects only some aspects of visual information to be processed to a high level. This 'mechanism' is known as selective attention and at some point or several points between the input and response of the visual system, information in a scene must compete for this attention.

One way in which information from the earlier, automatic stages of visual processing can be selected for processing at a high level is by 'attention capture'. Although automatic processing is generally considered to be limited or relatively 'low level' in nature it is able to establish the presence of potentially important visual information. For example, the presence of a stimulus which is very different

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[54] (bottom-up processing)

[55] The first stage of visual processing is characterized by Shiffrin and Schneider (1977) as occurring automatically, i.e., without the need for attentional resources and is fast, inflexible and relatively effortless.

[56] The reason behind such an organisation is thought to be due to the processing limitations of the brain. Despite the extensively distributed serial/parallel processing architecture of the visual cortex only a small amount of the available information coming through the afferent sensory systems can be processed at any one time. The ability to fully discriminate, identify and store in memory, independent objects at the same time is therefore limited. This limitation thought to be the result of the inherent limited processing capacity of the brain (Broadbent 1958, 1971, 1982). At any given time therefore only a small amount of the information available on the retina can be processed to a high level and used in the control of behaviour (Desimone and Duncan, 1995).

from the surrounding scene[57] is able to rapidly draw attention to its location. This appears to be an involuntary response which can also occur to the sudden appearance of a stimulus (Jonides and Yantis, 1988). The application of attention to the deviant stimulus enables it to be fully identified and interpreted.

The stimuli in the visual field can also be selected for higher level[58] analysis by top-down processes. Stimuli can be selected on the basis of spatial location, (i.e., position in the visual field, Posner, 1980) or other attributes such as speed, colour or form (i.e., featural attention) (Beauchamp, Cox and DeYoe, 1997; Treisman and Gormican, 1988) or task relevance (Kahneman and Treisman, 1984) or a combination of these characteristics (Grande, McGlinchey-Berroth, Milberg and D'Esposito, 1996).

This deployment of spatial attention to the area of 'potential interest' has been characterised as a mechanism analogous to a spotlight or zoom lens which concentrates high level processing resources on restricted portions of the visual field (Treisman and Gelade, 1980; Luck, Hillyard, Mangun and Gazzanniga, 1989). Such a mechanism enhances the processing of stimuli at locations that are currently attended (i.e. within the beam of the spotlight) compared to the information that is not attended (Posner and Cohen, 1984). Normally this highlighted region corresponds to the central portion of the visual field or foveal vision and can be adjusted in size by instructional set, i.e., top down processes and can be scaled up or down to accommodate for example a simple letter or an entire word[59] (Hoffman, Nelson and Houck, 1983; Laberge, 1983; Erikson and St James, 1986)[60]. To process several aspects of the visual field to a high level the serial deployment of attention is required, consecutively deploying attention to spatially different areas of the visual field (Shiffrin and Schneider, 1977).

Selective attention appears therefore to act as a 'filter' enabling only information that is potentially useful to pass onto later stages of processing (Steinman, Steinman and Lehmmkuhle, 1997 and Allport, 1993). Selective attention results therefore in the differential processing of simultaneous sources of information.

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[57] The competition for further analysis is weighted toward stimuli that differ from their background.
[58] I.e., higher visual functions such as perception, recognition, interpretation, identification, computing the spatial representations between objects, reading , storage and retrieval of stimulus information from memory and the processing of semantic information, Theeuwes (1994).
[59] I.e., one can bias the competition for attention among stimuli in favour of a particular item.
[60] Posner et al. (1987) have described selective attention as being made up of several component processes; (a) disengagement of attention from the current focus, (b) moving or shifting attention to a new focus and (c) engagement of attention at the new focus. These component processes appear to be mediated by different regions of the brain. The posterior parietal lobe, the superior colliculus and the pulvinar are involved in shifting attention. It is thought that the parietal lobe first disengages attention from its present focus; then the midbrain is active to move the index of attention to the area of the target and the pulvinar is involved in restricting input to the indexed area (Posner, 1995).

2.23 ANATOMICAL AREAS ASSOCIATED WITH AUTOMATIC AND ATTENTION - RELATED VISUAL PROCESSING

Attending to visual information can result in a measurable enhancement in its processing. Whether or not attention enhances the visual function associated with a particular region of the cortex has been taken to indicate whether that region is associated with automatic or attention-related visual processing.

Attention-mediated enhancement of visual processing does not appear to occur in all areas of the cortex associated with visual processing. Spatial attention does not appear to modulate the processing that occurs in the striate cortex (as no measurable enhancement in activity has been recorded when individuals are attending compared to not-attending to a visual stimulus). Attention-related enhancement has however been observed in many extrastriate areas and the association cortices.

Automatic visual processing appears to be a property primarily of the striate cortex and of extrastriate area V2. Attention-mediated processing however appears to be primarily a property of the higher level visual processing areas such as the parietal and temporal cortices, with extrastriate areas V4 and V5 exhibiting some attention-related modulation in function.

Whether attention modulates the processing of a particular visual area has been determined by performing single unit studies[61]. Moran and Desimone, (1985) and Haenny and Schiller, (1988) found that spatial attention increased the activity of neurones in V4. Treue and Maunsell, (1996) reported a similar attentional modulation for neurones in V5 and MST. Spitzer and Richmond, (1991) also found that the responsiveness of monkey inferior temporal lobe neurons was related to the degree of attention the animal paid to the stimulus. Wurtz, Goldberg and Robinson, (1980); Moran and Desimone, (1985); Haenny and Schiller, (1988) and Colby, (1991) found no evidence however that spatial attention increased the activity of neurones in the striate cortex. Single unit studies therefore tend to support the view that attentional modulation does not occur in the striate cortex (but see Motter, (1993) for a controversial report of attentional modulation in the striate cortex and Desimone and Duncan, (1995) for a criticism of it).

Electrophysiology has also been applied to determine whether attention modulates the processing of visual areas. Mangun, Hillyard and Luck, (1993) also found that ERP components related to processing in the extrastriate regions exhibited an increase in amplitude to attended stimuli whereas ERP components related to processing in the striate cortex were not affected by attention (i.e., there was no

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[61] Measuring the responses of single neurons in the different visual processing areas of monkeys to determine whether attending compared to not attending to a particular stimulus increases the activity of the neuron. It is generally accepted that if there is no difference in the response properties of the neurons involved, to attention, that attention has no effect on the visual processing of that region.

change in amplitude when evoked by attended versus unattended stimuli). This result is consistent with the single cell recordings reported earlier.

Positron emission tomography (PET) studies have also indicated that attention modifies (enhances) neural processing in the posterior and superior parietal cortex (Corbetta et al., 1993; Nobre, Sebestyen, Gitelman et al.,1997) and area V5 (Corbetta et al., 1991 and Haxby et al., 1991)[62]. In addition, Woldorff, Fox, Matzke, Lancaster, Veerasswamy, Zamarripa, Seabolt, Glass, Gao, Martin and Jerabek (1997) found that the V3 and V4 regions of the extrastriate cortex were modulated by spatial attention whereas the striate cortex was not (see also Mangun, Hopfinger, Kussmaul, Fletcheer and Heinze, 1997; Heinze, Mangun, Burchert, Hinrichs et al., 1994; Clark et al., (1997). The evidence that the activity of the striate cortex is NOT modified by attention appears to be robust (see also Hillyard et al., 1997)[63, 64].

The available evidence therefore indicates that the striate cortex is concerned with the automatic aspects of visual processing, whereas the majority of the extrastriate and association areas are primarily concerned with attention-mediated visual processing.

2.24 VISUAL FUNCTION IN ALZHEIMER'S DISEASE

It was evident from the review in chapter one that the pathological processes associated with AD, primarily affected the high level, attention-mediated visual processing areas of the temporal and parietal cortices compared to the striate cortex, concerned with automatic visual processing, which was relatively spared. The extrastriate visual areas which appear to form the intermediate levels of visual processing between the striate and association cortices were found to be affected by AD-related pathology to an extent which was intermediate between that affecting the striate cortex and the temporal and parietal

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[62] See also Beauchamp, Cox and DeYoe (1997); Buchel and Friston, (1997); O'Cravenet al., (1997); Beauchamp and De Yoe, (1996); Treue and Maunsell, (1996).

[63] Posner and Dehaene, (1994) suggested that a possible reason why striate cortex neurones do not appear to be modulated by attention is that along with the neurones of the retina and LGN, the striate cortex neurones already respond at a high firing rate to their preferred stimuli whether they are attended or not, i.e., there is automatic activation. In the later stages of visual processing, the neurone's responses become less automatic and therefore attention can have the effect of boosting the lower activity of these neurones coding for the attended stimulus. Posner and Dehaene go on to suggest that at cortical areas involved in the very high levels of visual processing (that activate only during specific tasks rather than in passive situations) attention appears necessary for any activation to occur.

[64] LaBerge (1995) has proposed a computational and anatomical model of visuospatial attention that incorporates current knowledge of visual system neurophysiology with evidence from human PET and ERP studies. In this model, spatial attention does not influence visual processing at the level of the striate cortex but rather acts to modulate the flow of information from striate to extrastriate areas. The pulvinar nucleus of the thalamus was ascribed the key role of selectively biasing information flow in extrastriate pathways by means of its reciprocal anatomical projections to these cortical areas.

cortices. One would predict therefore that because the striate cortex is relatively spared in AD (compared to normal ageing) then the automatic visual processing associated with the striate cortex should also be relatively preserved in AD compared to normal ageing.

By contrast, the greater pathological load evident in many of the extrastriate regions and the parietal and temporal cortices in AD compared to normal ageing, would suggest therefore the appearance of greater deficits in the attention-related visual processing associated with these areas in AD compared to normal ageing.

Indeed, tests of the visual functions associated with the extrastriate visual areas have been compared in AD and normal ageing. For example, Cronin-Golomb et al., (1991) measured colour vision and stereoacuity (which require intact extrastriate areas for normal performance, Zeki 1973; Pearlman et al., 1979) and found them impaired in AD relative to the age-matched controls (see also Kurylo, Corkin and Growdon, 1994). It was also found that individuals with AD had difficulty discriminating between blue-green stimuli on the stroop test (Stroop, 1935) (a cognitive measure which is interpreted as requiring intact colour vision in the extrastriate regions, Cohen et al., 1988; Fisher et al., 1990). Impairment in colour perception in AD relative to normal ageing has also been found by Cronin-Golomb et al., (1993). In addition, Silverman, Tran, Zimmerman and Feldon, (1994) found evidence for greater higher-level motion perception deficits in AD patients compared to age matched controls.

Many studies have also been performed whose results have indicated a greater detriment in the performance of the visual processing mediated by the association cortices in AD compared to healthy ageing. For example, recognising visually presented objects and familiar faces, environmental orientation, constructional drawing, copying and block assembly (Mendez, Mendez, Martin, Smyth and Whitehouse, 1990; Nobili and Sannita, 1997; reproducing composite drawings (Klekkoy, 1976) and identifying and locating complex stimuli (Levine, Lee and Fisher, 1993) have been found to be significantly impaired in AD compared to age matched healthy controls.

Kurylo et al., (1996) also examined whether the AD-related impairments of higher level visual function could be segregated on the basis of cortical visual pathways; i.e. between the dorsal and ventral pathways. Kurylo et al., tested individuals with AD and age-matched controls on eight tasks designed to probe the capacities associated with either the ventral or dorsal pathways, i.e. four tests of visuospatial abilities[65], designed to measure the function of the dorsal pathway and four tests of object recognition[66] designed to measure the function of the ventral pathway.

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[65] Mental rotation, road map test, stick test (reconstructing patterns of sticks) and discrimination of spatial position. For a detailed description of each test see Kurylo et al., 1996).

[66] Mooney closure faces test, Benton facial recognition, Wechsler adult intelligence scale-revised (WAIS-R) picture arrangement and discrimination of complex faces. For a description of each test see Kurylo et al. (1996).

The finding of an impairment in AD of both visuospatial abilities and object recognition, with a relatively greater deficit in object recognition, was interpreted by Kurylo et al., as supporting the hypothesis that the ventral pathway, specialised for object recognition is more affected in AD than the dorsal stream. These results are consistent with those from some histological studies in which a greater relative degeneration of temporal cortex, particularly the inferotemporal cortex, than of parietal cortex has been found in AD, for example, Bouras et al. (1994).

Cronin-Golomb et al. (1995) also found a differentiation between object recognition and spatial localisation abilities in AD. Based on the association between several visual tests and cognitive function they found that cognitive tests for which visual performance was the best predictor of dementia were those that assessed object recognition.

2.25 ALZHEIMER'S DISEASE-RELATED DEFICITS IN THE SHIFTING OF ATTENTION

In comparison to normal ageing, greater AD-related deficits in the mechanisms which control the ability to direct visuospatial attention have also been reported. The posterior parietal[67] cortex forms part of a widely distributed neural system (including the pulvinar and frontal cortex) that is involved in the shifting of attention from one spatial location to another (Posner and Dehaene, 1994). This brain region is hypometabolic in early AD (Haxby, Grady, Duara et al 1986) and has been associated with a greater attention-shifting deficit in AD compared to normal ageing (Parasuraman, Greenwood, Haxby et al., 1992; Greenwood, et al., 1997)[68] [69].

Studies by Oken, Kishiyama, Kaye and Howieson (1994) have illustrated that individuals with AD have disproportionate problems in shifting spatial attention compared with age-matched controls and problems also with the redirection of attention (Maruff and Currie 1995), (see also Grande, McGlinchey-Berroth, Milberg and D'Esposito, 1996, for a review).

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[67] The parietal lobes are thought to be involved in shifting or disengaging attention from previously attended locations. The right posterior parietal lobe appears to be specialised for directing attention to spatial locations and may also be specifically involved in disengageing selective attention (Buck et al., 1997; Corbetta et al., 1993, 1995; Nobre et al., 1997).

[68] (See also Morecroft, et al., 1993; Posner and Dehaene, 1994; Faust and Balota, 1997 and Greenwood and Parasuraman, 1994).

[69] In addition to impairments in visuospatial attention shifting, individuals with AD also exhibit deficits in shifting attention between different features (Haxby et al. 1991) or levels of organisation of a composite visual object (Filooteo, et al., 1992; Massman, et al. 1993). There is also impairment in shifting attention between visual and auditory modalities (Beradi, 1994).

Parasuraman, Greenwood, Haxby and Grady (1992) showed that compared with healthy age-matched controls, individuals with AD were selectively deficient in the disengagement of attention[70]. This finding has been replicated in subsequent studies by Maruff, Malone and Currie, (1995); Oken, Kishiyama, Kaye and Howieson (1994) and Scinto et al., (1994), (see also Greenwood et al., 1997).

In relation to normal ageing individuals with AD have also been found to exhibit impairments in shifting attention between different features (Haxby, Parasuraman, Gillette and Raffaele, 1991) or levels of organisation of a composite visual object (Filooteo et al., 1992; Massman et al., 1993). There is also impairment in shifting attention between visual and auditory modalities (Beradi, 1994) and from one stimulus set or categorisation rule to another (Grady et al., 1988; Sahakian, Sownes and Eagger, 1990).

Shifting between spatial locations and objects is impaired in early AD (Parasuraman and Martin 1994), whereas cue-driven focusing to a visual hemifield (Parasuraman, Greenwood and Haxby 1992) or to colour (Nebes and Brady 1989) is minimally affected.

Other studies on visual selective attention indicate that in AD the ability to select a target that occurs in the presence of one or more distractors is impaired (Sullivan, Faust and Balota 1995; Balota and Ferraro 1993). This suggests that when presented with conflicting stimulus information individuals with AD have more difficulty than older adults in selecting one of two available responses. This problem may be related to their ability to suppress the irrelevant dimensions of the stimulus.

One underlying factor which may influence the inhibitory function underlying selective attention in both older adults and AD is a degeneration of the cortically projecting cholinergic neurons of the nucleus basalis of Meynert. Although as described earlier, early studies attributed decreased cholinergic function to learning and memory deficits in older adults and AD, more recent studies suggest that the primary effect of the cholinergic system is on attention (Callaway, Halliday and Naylor, 1992; Meador et al 1993; Muir, Page, Sirinathsinghji, Robbins and Everitt (1993). Calloway et al propose that cholinergic activity narrows the focus of attention and that anticholinergics broaden it. Therefore cholinergic blockade impaired focused attention, as was shown by Meador et al 1993. Selective attention may therefore have a cholinergic basis.

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[70] There is modest slowing of the disengagement of attention up to about age 75 in healthy individuals (Greenwood and Parasuraman, 1994). This effect increases progressively with age so that older adults (75-85) are slowed more on invalid-cue trials than are adults under 75 (Greenwood and Parasuraman, 1994). The disengagement deficit is even more marked in AD patients (Parasuraman et al., 1992).

2.26 TESTS OF AUTOMATIC VISUAL FUNCTION IN AD

There has been some debate as to whether any of the deficits in high level visual processing in AD may in fact also be a product of deficits in the functional integrity of the retina and optic nerve (i.e. due to precortical neuropathological changes, Rizzo et al 1992).

Hinton, Sadun, Blanks and Miller, (1986) reported a significant loss of fibres in the optic nerve in AD and Blanks et al., (1989) and Blanks, Torigoe, Hinton and Blanks, (1996) reported significant retinal ganglion cell loss in AD compared to that found in normal ageing. However, the majority of histological, and electrophysiological studies have indicated that compared to normal ageing, the difference in neuronal degeneration, if any, is very slight in the retina and optic nerve in AD (Katz, et al., 1989; Cogan, 1979; Schlotterer et al., 1983; Nissen et al., 1985; Wright et al., 1987; Drucker and Curcio, 1993; Cronin-Golomb et al., 1991, 1993; Hof and Bouras, 1991; Rizzo et al., 1992; Curcio and Drucker, 1993; Nobili and Sannita, 1997).

Compared to the research into the higher level, attention-related visual processing in Alzheimer's disease some of which is mentioned above, the automatic visual processing associated with the striate cortex, has been less prominent. Compared to the areas which mediate attention-related, higher level visual processing, the striate cortex associated with automatic visual processing is generally reported as being spared in AD in relation to normal ageing. It is possible however that a functional deficit could occur in the absence of obvious pathological change in the striate cortex. It may be the case that previous measures of function have not been sensitive or appropriate enough to record such effects. Consequently, the possibility cannot be ruled out that changes in the automatic visual processing associated with the striate cortex, (from which projections go to all other visual processing areas either directly or indirectly), may contribute to the deficits in higher level visual processing.

It is important therefore to determine whether indeed it is the case that this relative sparing from pathological change is also reflected in the relative sparing of the automatic visual processing associated with this area.

Previous research performed in order to measure the integrity of the visual processing associated with the striate cortex in ageing and AD has employed the psychophysical technique of 'visual search' and the measurement of 'visual evoked potentials'.

As visual search will form the basis for one of the experiments in the present study its application to the measurement of automatic and attention-related visual processing in ageing and AD will be discussed in detail in chapter 4.

2.27 ELECTROPHYSIOLOGY

As electrophysiology will play a major part in the current study the following sections will introduce some of its associated theoretical aspects. Its role in the assessment of the visual processing associated with the occipital cortex, particularly the striate region, will also be discussed.

As visual stimulus information traverses the visual pathways, the activation of successive relays gives rise to a sequence of precisely timed evoked potentials that may be recorded from the scalp and displayed in the form of an electroencephalogram (EEG). The EEG consists of continuous voltage fluctuations caused by the spatial and temporal summation of excitatory and inhibitory post-synaptic potentials[71] from thousands of neurones generated in response to the stimulus[72]. The potential fluxes create currents and the passage of transmembrane currents into the extracellular fluids produces field potentials. These field potentials may spread some distance from the active neurones (depending upon the electrical conductance of the intervening fluids and tissues) and penetrate the cortical surface, skull and scalp, thereby producing recordable potentials detectable by surface electrodes (Kertesz, 1994).

2.28 VISUAL EVOKED POTENTIALS

Evoked potentials take the form of sequences of voltage deflections that are time locked to the occurrence of visual sensory or cognitive events. They are extracted from the ongoing EEG by signal averaging techniques. The resultant waveform, representing voltage against time, consists of a series of overlapping peaks and troughs that may be separated into relatively distinct components on the basis of polarity, latency and scalp distribution. The components are designated according to their apparent polarity (negative, N; positive, P) and peak latency (expressed in milliseconds e.g. P300, or serial order P3 [3rd])[73].

The characteristics of recorded potentials vary in terms of response properties with recording time and spatial location. Their scalp distribution is determined by the anatomic orientation of the neuronal generators, with the position of the measuring electrodes on the scalp determining the topographic pattern of activity recorded, (Skrandies, 1995; Jeffries, 1996). The latency of such potentials at the

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[71] (especially pyramidal neurons, Martin 1991).

[72] This is particularly the case when a large population of neurones having similar orientation are activated concurrently (Hillyard, Mangun, Woldorff and Luck, 1995).

[73] That brain potentials are often referred to as components reflects the idea that a peak has a special significance in that it reflects the time of maximum activity of an intracerebral generator. However, a voltage deflection on the scalp may result from the summation of activity of any number of generators.

different electrode locations indicates the timing of underlying neuronal activity; their amplitude indicates the net synaptic activity in the participating neuronal population[74].

Certain components of these brain potentials are sensitive to the physical properties of the stimulus, some are sensitive to subsequent processing and some are sensitive to both. Corresponding to the apparent psychological stages of processing, electrophysiological components are sometimes described as endogenous[75] or exogenous[76] evoked potentials (Donchin, Ritter and McCallum, 1978; Gaillard and Ritter, 1983). This controversial exogenous/endogenous dimension roughly correlates with time, such that in each sensory modality, exogenous components tend to occur at earlier latencies than do endogenous ones[77].

The clinical utility of visual evoked potentials (VEPs) is based upon their dependence on the integrity of certain areas of the brain. If such areas are damaged by the pathological processes associated with ageing and AD for example, some of the components are altered from normal. The VEPs used for clinical purposes tend to be elicited in response to luminance change (flash VEPs) and the onset and reversal of patterned stimuli (pattern VEPs).

The flash and pattern VEPs provide information about different aspects of visual function.

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[74] Brain potentials only provide a view of those cerebral events that are sufficiently synchronised and organized to create fields at the scalp: a great deal of cerebral activity occurs without generating electrical activity recordable at the scalp (Vaughan and Arezzo, 1992).

[75] Endogenous potentials are elicited in response to an external stimulus event, tending to be elicited in circumstances where an individual is required to distinguish a target from non-targets and they are generally assumed not to be influenced directly by the physical parameters of the stimulus (Goodin and Aminoff, 1992). The variance of their amplitudes and latencies are determined primarily by the psychological processes involved in the stimulus events.

[76] Exogenous components reflect responses evoked by stimuli external to the central nervous system (CNS); their variance is primarily determined by the physical characteristics of the stimulus (Gaillard, 1988) and they occur independently of the psychological context of the stimuli. As their elicitation is a consequence of the occurrence of an appropriate stimulus they are also referred to as sensory-specific obligatory components (Näätänen, 1992).

[77] The exogenous and endogenous categories are probably idealised extremes on a continuous scale. There may be considerable overlap of these components. For example, an endogenous component may modulate regions of a waveform containing exogenous components and may overlap with other endogenous components in time and distribution over the scalp.

2.29 PATTERN REVERSAL VISUAL EVOKED POTENTIALS

Pattern reversal VEPs provide information about sensory visual function. Any repetitive visual stimulus can be used to elicit a VEP, although the most widely used in clinical practice have been patterned achromatic stimuli. The optimum stimulus for the pattern VEP is border contrast, which is commonly obtained by the use of a reversing black and white checkerboard pattern. The checkerboard has constant luminance and contrast at a constant frequency and provides a complex stimulus (as a result of the presence of multiple harmonic frequencies in addition to the fundamental, Aminoff and Goodin, 1994). The stimulus type used in pattern VEP enables one to look at different aspects of visual processing. For example, larger checks and larger stimulation fields produce greater stimulation of peripheral vision, while smaller checks preferentially stimulate central vision (Halliday, 1982) as a result of the portion of the retina responsible for the VEP being dependent upon the spatial frequency of the stimuli (Meredith and Celesia, 1982).

The VEP to pattern reversal stimuli consists of an early negativity (N75) followed by a large positive wave (P100) which occurs about 100 ms after stimulus presentation and a subsequent negativity (N145) (Gilmore, 1995). All of these peaks are recorded over the occiput. It is the P100 component which tends to be employed in clinical testing as there is a high degree of waveform consistency and reliability among both healthy and patient populations (Chiappa, 1989).

The P100 component is thought to be generated by input to the striate cortex via the retinogeniculate visual pathway and predominates at occipital electrode sites (Ray et al., 1991). Reports by Lehman et al. (1982); Kawashima et al. (1992) and Onofrj et al. (1993) suggest that the generators of P100 are located in the extrastriate cortex, while Noachter et al. (1993) report that the source of the P100 is both the striate and extrastriate cortex. However, that the striate cortex in particular is the generator of the P100 is supported by findings by Corletto et al. (1967); Maier et al. (1987); Ducati et al. (1988) and in particular by Seki, Nakasatoo, Fujjita, Hatanaka et al. (1996). By using magnetoencephalography linked with MRI, Seki et al. determined that the P100 component was localised at the lateral bottom of the calcarine fissure in the striate cortex[78]. There is also the finding that in lesions restricted to the striate cortex, the P100 potential is absent or abnormal (Aldrich et al., 1987) and in lesions involving the visual association cortex this potential is spared (Bodis-Wollner et al., 1977).

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[78] Support for the occipital cortex as the generator of the P100 is derived from studies of hemifield stimulation which results in the elicitatiob of the largest P100 components over the hemisphere ipsilateral to the stimulated field. This paradoxical lateralisation has been attributed to the location of the striate cortex on the mesial surface of the hemisphere (Aminoff and Goodin, 1994). It has also been found that the P100 remains positive if the stimulus is restricted to the lower hemifield but reverses its polarity when the stimulus is in the upper hemifield which suggests that the cortical neurones which generated the P100 are retinotopically organised (see Butler, Georggiou, Glass, Hancox, Hopper and Smith, 1987) and therefore indicates visual processing at the striate or some part of the extrastriate regions as opposed to the higher level visual association areas.

2.30 THE FLASH VEP

The flash VEP represents the simplest stimulus, a transient change in luminance only. VEPs to various temporal frequencies of flashes can provide reliable and sensitive indicators of clinical and subclinical optic nerve pathology and retrochiasmal deficits (Tobimatsu et al., 1994). The latencies of the different components of this response are more variable and complex than those elicited by pattern stimuli.

The early components of the flash VEP (i.e. those occurring before 100ms) are thought to be generated in the striate cortex; this includes the flash P1 component (Wright, Harding and Orwin, 1984; Kushner et al., 1988)[79]. The components occurring after 100 ms, including the flash P2, are thought to be generated in the extrastriate regions (Ciganek, 1961;Vaughan, 1966; Ray et al., 1991) and in visual areas of the temporal cortex[80]. The flash P2 component therefore appears to reflect the integrity of higher cortical areas (Wright, Harding and Orwin, 1984).

2.31 VISUAL EVOKED POTENTIALS IN AGEING

The normal age-related degeneration observed throughout the brain is accompanied by an increase in the latency of both the P2 component of the flash VEP and the P100 component of the pattern reversal VEP compared to the values for young adults. Such results indicate the presence of age-related changes in both the extrastriate and striate cortices respectively (Celesia and Daly, 1977; Snyder et al., 1981; Boback et al., 1989; Ray, Meaddor, Loring, Murro, Buccafusco, Yang, Zamrini, Thompson and Thompson, 1991; Tobimatsu, Kurita-Tashima, Nakayama-Hiromatsu, Akaazawa and Kato, 1993; Emmerson-Hanover, Shearer, Crel and Dustman, 1994). There is controversy however as to how much change occurs (Gilmore, 1995[81]).

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[79] It was suggested by Wright et al., (1985) that if the striate cortex was the generator site for the flash P1 component, then the flash P1 component in healthy individuals would not be expected to be as large and well defined as the pattern VEP, as the work by Hubel and Wiesel has indicated that the neurones of the striate cortex give an optimum response to patterned stimuli. Wright et al., (1985) carried out normative studies and confirmed that this was indeed the case.

[80] The areas of the brain thought to primarily process the flash stimulus are those involved with the retinotectal pathway which projects from the optic tract to the SC, the pulvinar nucleus and to V2 (and other visual association areas).

[81] For example, Allison et al., 1979, 1984; Stockard et al., (1979) suggested a 2-4 msec increase in latency per decade after age 40 years for the pattern reversal P100 component, whereas Celesia and Daly, (1977) reported only a 2 msec increase per decade. The discrepancies are probably the result of varying stimulus conditions.

The age-related changes are thought to be caused by a combination of decreased conduction velocity in the optic nerve and visual pathways secondary to myelin degeneration, axonal dystrophy, retinal ganglion cell degeneration, changes in neurotransmitter function, increased synaptic delay together with neuronal degeneration and loss in the lateral geniculate nucleus (LGN) the striate cortex and the extrastriate visual areas (Gilmore 1995).

2.32 VISUAL EVOKED POTENTIALS IN ALZHEIMER'S DISEASE

Several studies have been performed to determine to what extent Alzheimer's disease produces deficits in VEPs in addition to those seen in normal ageing. If according to the pathological and neuro-imaging studies it is indeed the case that the striate cortex is spared in AD in relation to normal ageing then one would not expect to see differences in the P100 component in AD compared to normal ageing.

The majority of studies have indeed found this to be the case. For example Philpot, Amin and Levy, (1990); Kiyosawa et al., (1989); Wright et al., (1986); Rizzo et al., (1992); Katz et al., (1989); Coben et al., (1983); Orwin et al., (1986) and Trick et al., (1989) found that the pattern P100 latency remained relatively unchanged in AD compared to normal ageing. Philpot et al., (1990) also found that the pattern reversal P100 component remained relatively unchanged by the severity of AD. Such findings indicated that the presence of AD in addition to ageing appeared not to result in any significantly greater deficit in the functional integrity of the striate cortex[82].

Partanen et al., (1994) did however find abnormalities in the pattern reversal P100 in AD compared to normal ageing, suggesting some additional functional deficit in the striate cortex in AD compared to normal ageing (see also the study by Sloan and Fenton, 1992).

Although Ruessman and Beneicke, (1991) and Ray et al., (1991) failed to find latency changes in flash VEPs in Alzheimer's disease, the majority of studies, for example, Coburn et al., (1991); Daniels, Harding and Anderson., (1994); Swanwick, Rowan, Coen, O'Mahony, Lee, Lawlor and Coakley., (1996); Wright et al., (1984); Wright and Furlong, (1988); Katz et al., (1989); Pollock et al., (1989); Philpot et al., (1990) and Aguglia et al., (1991) have produced evidence for the greater delay of the flash P2 component in AD compared to normal ageing. The flash P2 latency has also been observed to correlate with the severity of AD (Philpot et al., 1990)[83].

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[82] There appears to be no histopathological sign of differences in loss of retinal ganglion cells in AD compared to normal ageing and pattern electroretinograms have largely been found to be normal in AD compared to ageing (e.g., Strenn et al., 1991; Rizzo et al., 1992). Such findings indicate that any abnormalities found in pattern and flash VEPs in AD are probably not due to damage at the retinal level (Curcio and Drucker, 1993).

[83] The density of NFTs is low in primary projection areas such as the striate cortex, but increases in adjacent extrastraite areas and association areas. In laboratory monkeys, research has indicated that

According to Wright, Harding and Orwin, (1981) and Coburn, Ashford and Moreno, (1991) the selective delay of the flash P2 component reflects a deterioration of the cholinergic processing in the visual association areas in AD. Conversely, the normal latencies of earlier components of the flash VEP and the pattern P100 component in AD, indicate that the cholinergic neurons of the striate cortex remain relatively intact[84].

The measurement of P100 and P2 components has not however featured significantly in the clinical diagnosis of AD or of its progression. This is probably the result of the diversity in results both between and within individuals. The comparison of the results from different studies has also proved difficult because of the numerous different experimental techniques employed. Many of the earlier studies may also have suffered from the inclusion of individuals with varying stages and aetiologies of AD and the inclusion of individuals with an incorrect diagnosis. An example of this is seen in the studies by Ray et al., (1991) and Coburn et al., (1991), neither of which used the NINCDS-ADRDA criteria for the selection of individuals with AD (Swanwick et al., 1996). An additional problem is that VEPs are not immediately apparent in many individuals.

There is also some indication that results of VEP studies may not be specific to dementia of the AD type. For example, Sloan and Fenton (1992) recorded serial VEPs to flash and pattern reversal stimuli every six months over a two year period in older adults with AD, multi-infarct dementia (MID) and healthy older controls and found that the latency difference in the AD group was significantly greater than in the control group. There was however no significant difference in the VEPs between individuals with AD and MID (a result also found by Wright and Furlong, 1988). The flash VEP has also been reported to be delayed in aetiologically mixed groups of demented individuals compared to controls (Gilmore, 1995). Delayed flash P2 latency is also indicative of depression in older adults (Swanwick et al., 1996). Current evidence therefore indicates that on their own, VEPs are not sufficiently sensitive or specific, in the early stages of AD, to provide useful predictive information to the clinician (Swanwick et al., 1996).

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these regions appear to be sequentially activated during the brain's response to a flash stimulus (Coburn et al., 1993) and consequently would require the integrity of the cortico-cortical association neurons between these areas for the normal elicitation of the flash P2 component. The laminar and regional distributions of NFTs in AD imply deterioration of these corticocortical association fibres, which is consistent with evidence that the P2 delay occurs at some time after reception of the affferent volley by the primary cortical projection area (Coburn et al., 1993), suggesting therefore the disruption of transmission between the striate and extrastriate visual cortical regions.

[84] Further evidence for the association of cholinergic mechanisms and visual evoked potentials has been reported by Daniels et al., (1994) who, measuring flash VEPs found that the P2 latency was significantly increased for both individuals with Parkinson's disease (PD) taking anticholinergic medication and in individuals with AD. In addition, Bajalen et al., (1986) reported that the administration of a single dose of the anticholinergic drug hyoscine hydrobromide to young healthy individuals produced a significant increase in the latency of the flash P2 without altering the pattern reversal VEP. The hyoscine hydrobromide mimicked the effects seen in AD, suggesting therefore that a cholinergic defect may underlie the P2 delay in AD.

2.33 ELECTROPHYSIOLOGY AND AUTOMATIC STIMULUS PROCESSING.

The problems with VEP measurements outlined above mean that the extent of damage to the striate cortex in AD compared to normal ageing is difficult to determine by such methods. Consequently, prompted by such difficulties, an alternative method of measuring the integrity of automatic visual processing was sought.

A literature search for methods of measuring automatic sensory processing revealed that in the auditory modality automatic processing is assessed by measuring the production of an auditory event-related component called mismatch negativity (Näätänen, 1992). This measurement has been widely applied to the study of automatic auditory processing in clinical populations and has been shown to be sensitive to the changes in the brain associated with various neurological deficits.

Although several attempts had been made to determine whether a similar component could be evoked by the visual system a visual analogue had not been established. If it could be demonstrated that a visual analogue of this auditory MMN existed then it could provide a novel and informative method of determining the functional integrity of automatic visual processing in ageing and AD.

The aim of the present study was therefore to determine the existence of a visual analogue of the auditory mismatch negativity and if it could be established, to measure it in ageing and AD.

CHAPTER THREE: MISMATCH NEGATIVITY

3.1 INTRODUCTION

Auditory mismatch negativity (MMN) is a preattentional (automatic) response to discriminable stimulus change during repetitive auditory stimulation. Recorded even when an individual's attention is diverted from the stimulation, it takes the form of a negative augmentation of the N2 component of the auditory evoked potential.

Mismatch negativity has both theoretical (particularly in terms of automatic auditory processing and the 'level of selection argument') and clinical implications (its measurement has been found to differ from normal in several clinical conditions, for example, **ageing**, Woods, 1992; Pekkonen, Jousmaki, Partanen and Karhu, 1993; **Alzheimer's disease**, Pekkonen, Jousmaki, Kononen, Reinikainen and Partanen, 1994; **Schizophrenia**, Javitt, Doneshka, Grochowski and Ritter, 1995 and **coma patient prognosis**, Kane, Curry, Butler and Cummins, 1993).

The discovery of a visual analogue of the auditory mismatch negativity could have similar theoretical and clinical utility. Before discussing the theoretical basis behind the possible existence of a visual analogue of the auditory MMN, and the methods the present study will employ to try and elicit it, the following sections will provide a review of auditory MMN in historical, theoretical and clinical terms. This will provide a clear picture of what auditory MMN is and consequently, what predictions we can make for its visual analogue.

The aim of the study was to attempt to elicit a visual analogue of the auditory mismatch negativity (MMN) in young healthy adults; if successful, the visual mismatch negativity would be measured in older adults and older adults with Alzheimer's disease.

3.2 THE HISTORICAL BASIS OF AUDITORY MMN: AUDITORY SELECTIVE ATTENTION.

Because event related potentials (ERPs) can non-invasively trace the flow of sensory information through the afferent pathways with a high degree of temporal resolution they have been applied to the study of information processing and theories of attention, particularly concerning the level of processing at which selective attention occurs. By measuring the timing of attention-induced modifications in stimulus evoked ERPs and specifying the brain areas in which they occur, strong inferences have been made about the level of processing at which selectivity is imposed. It was from such research in the auditory modality, that the existence of the auditory mismatch component of the auditory (ERP) was established.

3.3 AUDITORY LEVEL OF SELECTION; HILLYARD versus NÄÄTÄNEN

Hillyard and colleagues (see Näätänen, 1992 for a review) proposed that the selection of stimuli to be processed to a higher level occurred at a very early stage of auditory processing, where stimuli are selected or rejected according to whether or not they posses a simple sensory attribute that defines the attended stimulus channel. Hillyard and colleagues characterised auditory selective attention as selectively biasing or gating auditory stimulus processing by acting as a gain control (amplification) process that increases the strength of a selected sensory input, before full perceptual analysis has occurred, so that only those stimuli that are attended receive high level processing (e.g. Hillyard, 1981).

Näätänen and colleagues (see Näätänen, 1992 for a review) however, proposed that the differential processing of attended and non-attended stimuli does not occur as early, (i.e., in the sensory pathways) as Hillyard and colleagues suggested. Näätänen and colleagues suggested that all physical auditory stimulus features are processed automatically (i.e., that attention does not modulate initial stimulus representation in audition) and that selection for further, higher level processing, occurs later.

Auditory ERP studies have been widely employed in an attempt to determine the level of selection. If as Hillyard and colleagues propose, selective attention occurs very early in auditory sensory processing, then stimuli that are attended (i.e. possess the appropriate characteristics), should result in the enhancement[85], of the corresponding sensory-specific (exogenous) components known to reflect the brain's response to auditory physical stimulus features, compared to when the same stimuli are not attended. If however, as according to Näätänen and colleagues, all physical stimuli are processed irrespective of attention, then there should be no modulation of the amplitude of such components with attention.

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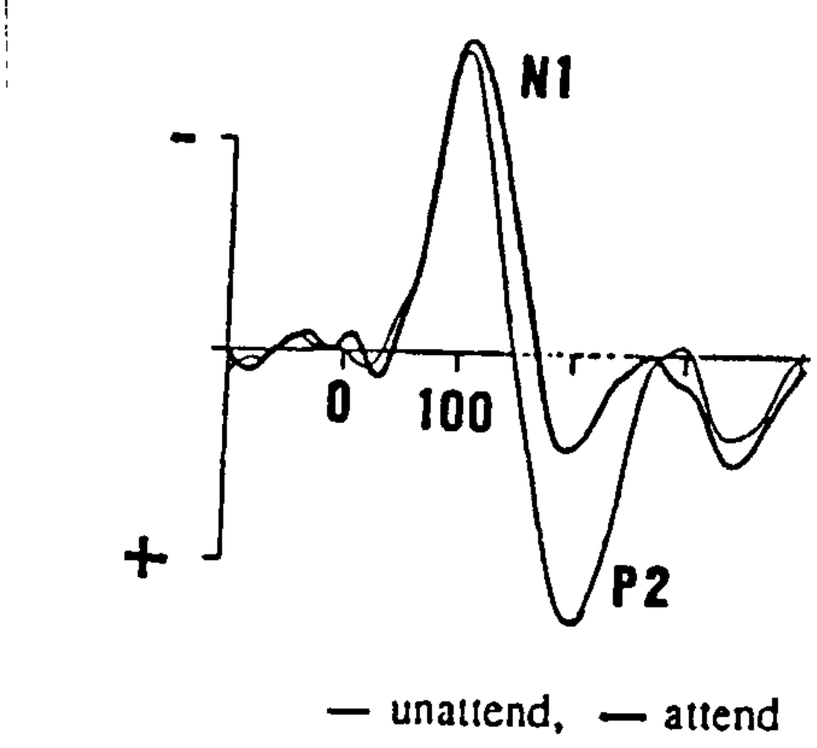
[85] (increase in amplitude with little or no change in wave shape or generator source localisation)

To determine whether attentional modulation of exogenous components occurs the 'oddball' experimental technique has been widely employed, where ERPs are recorded in dichotic listening tasks. Randomised sequences of tones are presented to the left and right ears at a rapid rate. The tones in the two ears differ in pitch and a fraction of the tones (the targets) differ slightly in some parameter such as duration or intensity, from the more common standard tones. The participant's task is to pay attention to the tones in one ear at a time and to detect occurrences of the 'difficult-to-detect' targets in that ear. There are active and passive forms. In the active condition the participant is asked to respond to designated target tones and in the passive condition the participant's attention is directed elsewhere and the participant is not required to make any overt response to these auditory stimuli (Lavikainen 1997, Näätänen, 1990).

It is the auditory exogenous N1 component, indicated in figure 3.1, that has figured predominantly in the argument about whether attending to a particular stimulus feature increases the amplitude of exogenous ERP components compared to the same feature when it is not attended.

Figure 3.1 The Auditory ERP To Attended Versus Non-Attended Auditory Stimuli At Electrode Site Cz (From NääTäNen, 1992).



N1 denotes a negativity that usually peaks at about 100 msec from stimulus onset. P2 indicates a positivity that peaks around 180-200 msec. N1 is preceded by a small positivity, P1, which peaks at about 50 msec, (Näätänen, 1992; Näätänen and Picton, 1987). The primary auditory cortex is thought to be the generator of the auditory N1, which is elicited by any discrete auditory stimulus[86].

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[86] The N1 does not reflect a unitary response to the eliciting stimulus, but rather several sub-processes that are differentially sensitive to different parameters, with contributions from as many as six separate brain processes. The first three N1 components are controlled by the temporal and physical aspects of the stimulus and the general state of the individual and the three later components, viz, the MMN and the temporal and frontal components of the PN (to be discussed later) depend principally on the conditions in which the stimulus occurs (Näätänen and Picton, 1987; Teder, Alho, Reinikainen and Näätänen, 1993).

Hillyard, Hink, Schwent and Picton, (1973) found that the vertex N1 deflection was larger in response to attended than non-attended stimuli; evident as early as 60-70 msec post stimulus. Hillyard et al., (1973) used very short ISIs, with left ear tones of a considerably higher pitch than the right ear tones to force their participants to attend exclusively to relevant stimuli. Both inputs included occasional, randomly placed, slightly higher-pitched tones which were to be counted in a designated ear. The difference in negativity between the attended and unattended stimuli was termed the negative difference (Nd) [87], with the negativity surrounding the N1 component region known as the early Nd.

Hillyard et al. (1973) regarded this enhancement of the N1 component to attended auditory stimuli as indicating the operation of a sensory gain control mechanism, where the physical features of only selected stimuli are processed (i.e. a stimulus selection process which enables stimuli to be selected or rejected according to whether or not they possess a simple sensory attribute that defines 'what is to be attended') and consequently gives preferential access to stimuli that are attended[88].

However, Hillyard et al's., (1973) interpretation of the N1 effect in terms of an enhancement of its generator process was questioned by Näätänen, (1975), who suggested that despite the short onset latency of this effect, it was endogenous in nature. Näätänen suggested that the attention effect could be accounted for by the overlap of a separate endogenous (i.e. later) attention-related negativity known as processing negativity (PN). Processing negativity has a duration of several hundred milliseconds and is recorded over the vertex of both right and left auditory cortices (Näätänen, Gaillard and Mantysalo, 1978). According to Näätänen, (1982) the PN is a reflection of the processing undergone by stimuli, which on the basis of certain pre-set physical stimulus criteria (which are stored and maintained for a short time in working memory [attentional trace]), are selected for higher-level processing.

According to Näätänen et al., (1978) the PN is an endogenous component generated by a cerebral mechanism different from that of the N1 component[89]. Näätänen therefore suggested that Hillyard et al's (1973) N1 attention effect may be a consequence of the attention specific PN component being superimposed on the attended ERP, causing an artificial increase in its measured amplitudes, rather than by an intensification of the generator process of the N1 (Näätänen, 1992).

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[87] Negativity indicates an increase in processing by the cerebral cortex.

[88] Hillyard et al., (1973) interpreted this finding as reflecting Broadbent's (1971, 1979) 'stimulus set' mode of attention, where only the sensory input to the attended channel is admitted for further analysis.

[89] If the same neural representation is activated by attended and unattended stimuli, but to different degrees, the associated evoked response should differ only in amplitude. The analysis of attended inputs via separate, specialised neural circuits would lead to ERPs that differ qualitatively in waveform and localisation. Attended tones elicit a more prolonged negative ERP (the PN) that appears to reflect activation of separate endogenous neural populations specialised for processing attended inputs (Näätänen, 1992).

Näätänen et al., (1978) demonstrated that such an endogenous attention effect, i.e. an ERP index of selective attention, can occur at latencies short enough to overlap with the exogenous N1, causing its artificial enlargement as a result of summation (Näätänen, 1982, 1990, 1992). Evidence in support of Näätänen's proposal was made in response to the results observed from a number of studies showing that the scalp topography and amplitude variations of the early Nd can be dissociated from those of the unattended N1 wave (Näätänen and Michie, 1979; Näätänen et al., 1992; Teder et al., 1993; Woods, Alho and Algazi, 1994). According to Näätänen and colleagues, the N1 is unaffected by attention and consequently suggest that attention does not modulate initial stimulus representation in audition.

Of course, the fact that the early Nd can differ in scalp distribution from the sensory evoked N1, does not necessarily indicate that this attention-related negativity is exclusively or even primarily endogenous in nature. Because the N1 is known to consist of multiple overlapping subcomponents, it is quite possible that attention could enhance the amplitude of only one or a subset of the evoked N1 generators while leaving the others unchanged. Such a selective enhancement would very likely result in an Nd that differs in scalp distribution from the overall unattended N1. The question has proved difficult to resolve because both the evoked N1 and the Nd attention effect are composed of multiple subcomponents that arise from concurrently active neural generator sources on the auditory cortex (Näätänen and Picton, 1987; Woldorff and Hillyard, 1991).

This controversy continues with much research and debate on both sides and detailed reviews can be found in Näätänen, (1992); Näätänen et al. (1992) and Teder et al. (1993). What is most important in terms of the present study is Näätänen's interpretation of the processing negativity; specifically its association with auditory mismatch negativity.

3.4 PROCESSING NEGATIVITY AND THE ATTENTIONAL TRACE THEORY OF AUDITORY SELECTIVE ATTENTION.

Näätänen, Gaillard and Varey, (1981) found two partially overlapping, successive components of the auditory PN; an early central one commencing at the N1 time zone, with a centro-frontal amplitude maximum and a later, much larger frontal component of long duration, maximum at frontal electrodes at 300-400 msec latency[90].

Näätänen, (1982) suggested that the early component of the PN reflected the initial selection of stimuli, where relevant stimuli are accepted for further processing and irrelevant stimuli are rejected. The late PN component persists well beyond the latency at which individuals make a decision about the

[90] The existence of two PN components had previously been suggested by Näätänen and Michie, (1979) who described an early, modality-specific component with short onset latency and a later, frontal component, with later onset (evident between 500-1000 msec after stimulus onset).

identity of the stimulus, so appears to be related to strategies or planning aspects of information processing rather than stimulus-elicited processing (Karayanidis and Michie, 1996). This second PN component is therefore thought to represent either the further processing of stimuli accepted in the initial selection, or the maintenance of the selective-attention state (Näätänen, 1982). So according to Näätänen (1990, 1992) the PN represents a cerebral 'matching' process by which the brain selects relevant from irrelevant stimuli for further processing.

Näätänen, (1982, 1985) proposed that task relevant, or to-be-attended stimuli, are represented by a voluntarily or actively maintained neuronal representation (which he termed the 'attentional trace') of the physical features of the pre-determined, relevant stimuli. According to Näätänen, the formation of such a trace requires several examples of the relevant stimulus to be presented and cannot be maintained in the absence of relatively frequent sensory reinforcement provided by these stimuli. The attentional trace therefore only encodes, stores and continually reinforces, task-relevant or to-be-attended features, Ritter, (1995).

Selection is then thought to occur as a result of a matching or comparison process in which sensory input is compared or matched with this voluntarily maintained representation of the relevant stimulus and ensures that only stimuli matching the attentive trace (i.e., relevant stimuli) are accepted for further processing. According to Näätänen, (1982, 1990) it is this process of matching between auditory input and the attentional trace, which generates the early PN component (with relevant stimuli that perfectly match the attentional trace eliciting the largest and longest duration early PN components)[91]. The attentional trace therefore underlies the acceptance of the to be-attended stimuli and the rejection of other stimuli.

3.5 NEURONAL REPRESENTATION OF AUDITORY STIMULI AND MISMATCH NEGATIVITY.

A neuronal representation of physical auditory features similar to that which results in the processes underlying the elicitation of the PN is also formed in response to common, repetitive auditory stimulation. When an auditory stimulus, with a particular physical characteristic (a specific frequency for example), is repeatedly presented, a neuronal representation of this physical feature is produced. If during the presentation of this so-called common or standard stimulus, an auditory stimulus with a discriminably different frequency is presented, (i.e. which is physically deviant from the common

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[91] Näätänen, (1992) further suggested that the early PN might reflect the increased neuronal firing which continues as long as the sensory input remains within the range of the attentional trace (i.e., proceeds within the facilitated part of the receiving system) and that the later PN component possibly reflects the frontal executive mechanism receiving information of the occurrence of a match between a relevant stimulus and the attentional trace (e.g. Näätänen and Picton, 1987).

stimulus) the comparison of its neuronal representation with that of the common stimulus results in a mismatch. This mismatch of neuronal representations, according to Näätänen, (1990) results in the elicitation of an electrophysiological component called the auditory mismatch negativity (MMN) (which appears as a negative augmentation of the N2 component of the auditory ERP) and serves to signal change or deviance within the auditory environment. The finding that MMN could be elicited whether individuals attended to the stimuli or not and without the deviant or standard stimuli being explicitly specified, led to the interpretation that MMN automatically or pre-attentively registered stimulus change, Ritter, (1992).

The fact that MMN is elicited independently of attention was interpreted by Näätänen and colleagues as indicating that neural traces or representations, encode all auditory stimulus features whether they are attended or not, otherwise no mismatch would occur. This was also interpreted by Näätänen as providing further evidence for the 'late-selection' position, where auditory stimuli are processed to a high level even in the absence of attention.

So, like the PN, the MMN reflects the function of a neural process which compares all auditory stimuli to a neuronal model of the physical features of repetitive stimuli (Lavikainen, 1997), but unlike the PN, reflects a mismatch or a change from the relevant or frequent stimulus and is independent of attention.

3.6 MISMATCH NEGATIVITY AND SENSORY (ECHOIC) MEMORY

The neuronal or attentional trace necessary for the elicitation of both PN and MMN is according to Näätänen, synonymous with echoic memory, with support provided by studies where standard (frequent) and deviant (infrequent) stimuli are presented at different interstimulus intervals (ISIs). No MMN is elicited when long interstimulus intervals (ISIs) or stimulus onset asynchrony (SOAs), are employed, for example 10 seconds or more, which matches the approximate decay time of echoic memory (Mäntysalo and Näätänen, 1987; Botcher-Gander and Ullsperger, 1992; Sams, Hari, Rif and Knuutila, 1993; see Näätänen, 1992 for a review)[92].

However, in principle, an underlying memory comparison process is not needed to explain MMN. The elicitation of MMN could be the result of a differential state of refractoriness (sensory adaptation or fatigue) between neuronal populations sensitive to the features of the standard and deviant stimuli.

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[92] Further support for the echoic or memory trace interpretation of MMN elicitation is that it is well known that a sensory memory representation of a stimulus can be prevented from developing by presenting an appropriate masking stimulus in close succession. Similar masking inserted in the MMN paradigm appear to prevent standards from developing their neural traces, as suggested by the failure of deviant traces to elicit MMN (Winkler, Reinikainen and Näätänen 1991).

It is possible that in the course of stimulus presentation, neurons responsive to deviant stimuli remain responsive, owing to long intervals (ISIs) between consecutive deviant stimuli, whereas neurons responsive to the standard stimulus frequency, become strongly refractory because of the fast rate of stimulus presentation. MMN could therefore be generated by new afferent elements, those corresponding to the frequency of the deviant rather than standard stimulus. Ullsperger and Baldeweg (1990) suggest that MMN reflects a neural process which indicates to higher processing levels, the deviance of the actual stimulus from the currently adjusted adaptation level[93].

However, the refractoriness explanation is questioned by several experimental results [94]. It is possible that both deviance detection mechanisms may be involved (Lavikkainen, Huotillainen, Ilmoniemi, Simola and Näätänen, 1995).

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[93] Ullsperger and Baldeweg (1990) suggest that the role of sensory adaptation should not be overlooked. They describe how from the viewpoint of sensory physiology, adaptation plays an important role and this should not be confused with refractoriness and fatigue. It is well known that, because of adaptation, the absolute threshold is adjusted to mean stimulus intensity. On the whole, however, adaptation effects an adjustment of the working range of the sensory organ, the working point moves to the steepest part of the dynamic characteristic curve with the highest sensitivity to stimulus differences (Kiedel, 1973). Helson (1964) stated that adaptation represents a mechanism for acquainting us with changes in the environment. He demonstrated in the framework of his adaptation-level theory that in addition to the various phenomena of adaptation among sensory systems, there are comparable adaptive phenomena in the central nervous system at all levels of information processing and at the behavioural level as well. Ullsperger and Baldeweg (1990) propose as an alternative to the memory trace explanation that the MMN reflects the distance of a stimulus from the current level of sensory adaptation rather than the distance between memory traces of consecutive stimuli per se. Both standard and deviant stimuli contribute according to their frequency of occurrence to the formation of the current adaptation level.

[94] That the MMN may not just be a response generated by new, non-refractory, afferent elements activated by an occasional infrequent (deviant)stimulus is suggested by: (1) The lack of a MMN-kind of response to the first stimulus of a sequence (Cowan, Winkler, Teder and Näätänen, 1993) and to stimuli presented with very long ISIs (Mantysalo and Näätänen, 1987; Kraus et al., 1993; Näätänen and Alho, 1995). Thus the MMN is elicited not by no stimulus per se; not even by infrequent ones. This indicates that a response specificity associated with stimulus change is involved. The MMN is elicited by a decrement in stimulus duration or loudness (it appears paradoxical that larger responses are obtained when stimulus energy is reduced and suggests that the cerebral mechanism involved responds to stimulus difference rather than to stimuli per se, Näätänen et al., 1989b; Paavilainen et al., 1991; Näätänen et al., 1993). (2) The elicitation by the omission of an element of a compound stimulus (Nordby et al, 1991; Winkler and Näätänen., 1993) or the second of two paired stimuli (see Näätänen and Alho 1995). Strong evidence also comes from the finding that MMN is prone to backward masking (Winkler, Reinikainen and Näätänen, 1993) and that it is elicited when the refractoriness state is controlled for, Shröger and Wolf, 1996a). So rather than by mere activation of fresh afferent elements, MMN is generated by a process that registers, i.e. is a neural code of, the stimulus difference or change. This would implicate the existence of a memory representation of the standard stimuli (Näätänen et al., 1989a,b). Näätänen (1984) suggested that there may be a distributed set of memory neurons that are maintained in a sustained state of inhibition by the repetitive standards whereas the surrounding regions are maintained in a state of tonic disinhibition. Thus any stimulus deviating in physical properties from the standards would activate a portion of the disinhibited cortical regions and generate a MMN.

3.7 THE TYPE OF AUDITORY STIMULI THAT CAN ELICIT THE MISMATCH NEGATIVITY

Mismatch negativity is elicited by change or deviance in the physical attributes of sound and their fundamental variations, such as: **increment or decrement in frequency** (Näätänen et al., 1978; Sams, Paavilainen, Alho and Näätänen., 1985b), **intensity** (Näätänen, Paavilainen, Alho, Reinikainen and Sams, 1987b, 1989), **duration** (Näätänen, Paavilainen and Reinikainen, 1989b) **real or apparent spatial locus of origin** (Paavilainen, Karlsson, Reinikainen and Näätänen, 1989), **changes in elements of tone pairs and other complex phonetic stimuli**, see Saarinen et al. (1992); Csèpe, Pantev, Hoke, Ross, Hampson (1997), Paavilainen et al. (1995); Aulanko, Hari, Lounasmaa, Näätänen and Sams, (1993); Aaltonen, Niemi, Nyrke, Tuhkanen (1987); Sams, Aulanko, Aaltonen and Näätänen (1990); Nordby, Roth and Pfefferbaum (1988 a and b); Schröger, Näätänen and Paavilainen (1992); Alho, Tervaniemi, Huotilainen, Lavikainen, Tiitinen, Illmoniemi, Knuutila and Näätänen (1996) and Tervaniemi, Alho, Paavilainen, Sams and Näätänen (1993). Although MMN is elicited by both simple and complex changes in auditory information as yet the effective deviations do not appear to include semantic properties.

3.8 THE EXPERIMENTAL ELICITATION OF MMN

MMN is elicited experimentally by performing selective attention tasks involving dichotic stimulus presentation at a fast rate. The participant's task is to attend to the input to a designated ear, (the attended channel) in order to detect occasional deviant stimuli (targets) in the stimulus sequence and to ignore the concurrent but irrelevant stimulus sequence (including deviant stimuli that are physically equivalent to the targets) input to the opposite ear (the unattended channel).

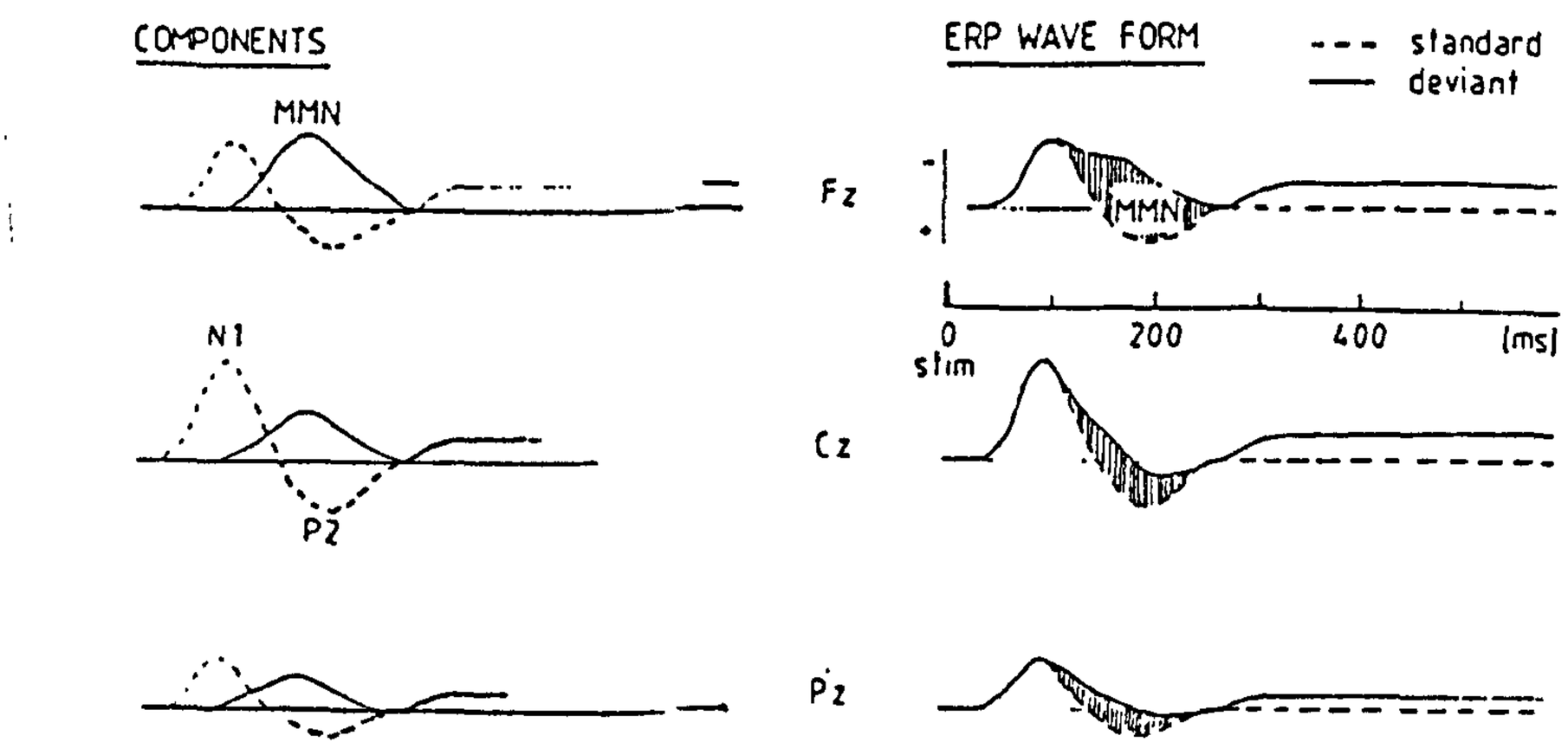
The deviant stimuli in both the attended and unattended stimulus sequences elicit a negativity which is not seen in response to the standard stimuli (Näätänen et al., 1978). This so-called mismatch negativity which is ramp-like and modality-specific, commences at about 80-250 msec from stimulus onset and peaks at about 150-250 msec (Jaaskelainen et al., 1996). The MMN was isolated from the N2 deflection of the ERP (presumed to reflect stimulus deviance or target discrimination; Squires and Hillyard, 1975) by Näätänen, Simpson and Loveless (1982) who divided the N2 wave into the MMN (N2a) and the N2b components.

The MMN-associated waveform differs depending upon whether or not the infrequent stimulus changes are attended to or not. In non-attend conditions, the deviant stimulus elicits a simple ERP with few

components; the N1[95] and P2 components being overlapped by the frontally dominant MMN. In attend conditions, the MMN is overlapped in turn by the N2b-P3a complex[96] which is thought to represent the recognition of particular stimuli, (Näätänen et al, 1982, Näätänen et al., 1993). Figure 3.2 (A) and 3.2 (B) indicate the difference in MMN in attend and non-attend conditions.

Figure 3.2 (A) Auditory MMN And Other Components In Non-Attend Condition

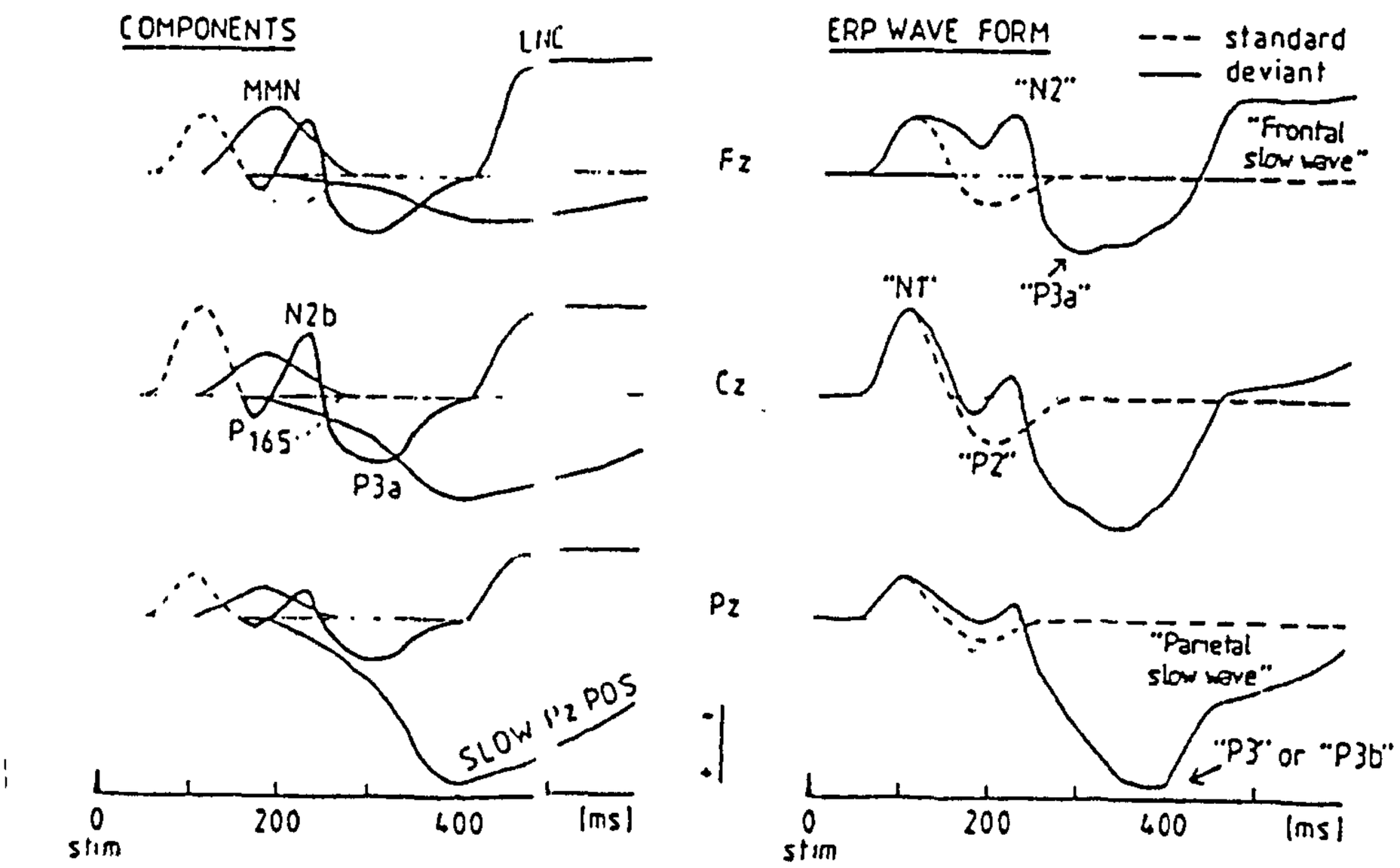
A simplified schematic illustration of the frontal (Fz), vertex (Cz) and parietal (Pz) ERPs (right side) to standard (dashed line) and deviant (solid line) stimuli and the corresponding ERP components (left side) in the oddball paradigm. (From Näätänen, 1992).



[95] The MMN follows the N1 in the auditory ERP so closely that they often overlap each other. The MMN, although lasting longer than N1, may start at the same latency.
[96] This is therefore not a good way to illustrate MMN.

Figure 3.2 B) Auditory MMN and Other Components in Attend Conditions

A simplified schematic illustration of the frontal (Fz), vertex (Cz) and parietal (Pz) ERPs (right side) to standard (dashed line) and deviant (solid line) stimuli and the corresponding ERP components (left side) in the oddball paradigm, (from Näätänen, 1992).



3.9 OTHER COMPONENTS ASSOCIATED WITH MISMATCH NEGATIVITY

The modality-specific N2b component (only elicited when attention is directed to the deviant target stimuli) is a sharp negative component of a longer latency and a more posterior distribution than the MMN. It is thought to reflect activity in both sensory association and multimodal association cortices (e.g. see Näätänen and Picton 1986(a) and Näätänen and Gaillard 1983, for a review). The N2b is *not* related to stimulus significance as it is elicited by both target and non-target deviants (Alho et al., 1990), but is instead thought to reflect the active stimulus discrimination associated with controlled processing. The N2b component is associated with a subsequent late positive P3 wave (Näätänen and Gaillard, 1983; Näätänen, 1986, 1988) and is therefore usually referred to as the N2b/P3a complex; the two waves forming a vertex response.

The P3 deflection has been divided into P3a and P3b. P3a is thought to signal attention switch (Näätänen et al., 1982) or the registration of a novel signal (Squires et al., 1975) and is largest at

frontocentral sites. P3b, (or slow parietal positivity), may be related to stimulus significance (or the further evaluation of the stimulus), Näätänen et al. (1982).

There have also been observations of a later negativity following an MMN (Alho et al., 1992), peaking at about 400 msec. It was not caused by an attention-related N2b component because, like the preceding MMN, it was elicited in non-attend tasks of varying difficulty and attentional demands. A later negativity following the MMN to frequency change in unattended tones was also observed by Näätänen et al. (1982; see also Näätänen, Sams, Jarvvilehto and Soininen, 1983, who suggested that this negativity might be associated with a 'sensitisation process' after the occurrence of a stimulus change, which elicits the MMN but does not trigger any subsequent endogenous processes. Näätänen et al., also suggested that this 'sensitisation process' might be automatic preparation for detecting possible subsequent stimulus changes (Alho, 1995).

3.10 GENERATOR SOURCES OF THE AUDITORY MMN

Both electrical and magnetic recordings together with animal and lesion studies have identified the auditory cortex (on the superior surface of the temporal lobe), as the major origin for the human MMN (Alho, 1995). In addition to this bilateral supratemporal auditory cortex generator of MMN, there also appears to be contributions from several other areas of the brain. The existence of a frontal generator has been reported by (Näätänen and Michie, 1979; Scherg, Vajsar and Picton, 1989; Giard et al., 1990; for a review see Näätänen, 1992 and Alho, 1995). Csèpe, Karmos and Molnar (1989) have reported the results of intracranial MMN recordings in animals that suggest that in some species at least, MMN sub-components may also be generated in the thalamus and hippocampus (see Alho, 1995 for a review).

In addition, larger amplitudes of MMN have been found over the right compared to the left hemisphere irrespective of the ear of stimulation. This finding, according to Lavikainen (1997) implies that there may be another subcomponent of the MMN in the temporal brain areas, possibly arising from the secondary auditory cortex or the association cortex.

3.11 (A) THE SUPRATEMPORAL MMN COMPONENT.

According to Näätänen and Michie (1979), the supratemporal MMN reflects the automatic comparison of incoming stimuli to a neural trace representing the physical features of repetitive aspects of the environment and therefore reflects a sensory specific process responsible for the automatic analysis of stimuli and therefore of stimulus change detection.

Recent studies have indicated that deviants of different physical attributes of auditory stimuli, such as frequency, intensity, duration and phonetic change, that form the determinants of MMN, are processed in spatially different cortical areas (Paavilainen et al., 1991; Giard, Lavikainen, Reinnikainen, Perrin, Bertrand, Pernier and Näätänen, 1995; Aaltonen et al., 1993). Such a finding suggests that the MMN generator locations in the auditory cortex differ according to the deviant stimulus features. This implies adjacent but partly different neuronal populations or neuronal representations for different features. Microelectrode studies in cats have also shown different topographic mapping for frequency and intensity (Phillips and Orman, 1984; Phillips, Orman, Musicant and Wilson, 1985; see also Schreiner, Menndelson and Sutter, 1992).

The existence of such feature-specific generator locations has also been supported by findings that the MMN obtained with two-dimensional feature changes (such as frequency and location, frequency and duration and duration and intensity) are equal to the sum of the MMNs elicited by the corresponding one dimensional changes (e.g. Kurtzberg, Kreuzer, Fliegletr, Ritter and Vaughan, 1996). This finding can be explained best by the hypothesis that in the case of a two dimensional deviant, each feature-change elicits its own MMN. According to Shröger (1997) such findings point to the existence of a completely modular organisation of underlying memory representations, and indicate that different features are stored in different regions of the brain thus enabling features to be mismatched in parallel. However, such findings do not prove that these representations are isolated feature-specific traces, as they may be connected and the way these connections are organised may determine the formation of auditory objects. For example, second order features (such as particular frequency-intensity conjunctions) may be established by some Hebbian-like connected networks (Pulvermuller, 1996) together with the possibility of cross talk between feature traces (Czigler and Winkler, 1996 in Schroger, 1997).

3.11 (B) THE FRONTAL MMN COMPONENT

According to Näätänen and Alho, (1995) and Jaaskelainen et al. (1996), the frontal component of the auditory MMN is associated with the involuntary orienting of attention which leads to the conscious discrimination of change in the auditory environment. To become aware of a deviant, a variable threshold may have to be exceeded by the mismatch signal. The intention to detect deviants consciously may also reduce the threshold, whereas engagement in some demanding primary task increases the threshold

Although there is no direct experimental proof of this hypothesis, it seems plausible because of the finding that an attention switch toward the irrelevant deviant (indexed by the P3a) is elicited by large deviants when the primary task is not very demanding (e.g. Näätänen et al., 1982; Sams et al., 1985) but not when the primary task is highly demanding (Alho et al., 1994). However, in the case of

unexpected novel events such as environmental noises, the mismatch signal may be strong enough to pass the threshold even with highly demanding primary tasks (Shröger, 1997).

However, in spite of the theoretical and practical implications of the frontal MMN component its existence has been questioned. As reported by Alho, Woods, Algazi, Knight and Näätänen (1994) it has been difficult to disentangle the relative contributions of frontal and auditory cortex to MMN generation because of temporal and distributional overlap (Giard et al., 1990). While the frontal subcomponent would be expected to have an amplitude maximum at frontal scalp sites, the auditory cortex subcomponent of the MMN might also be largest at frontal sites because of generator orientation (see Tiitinen et al., 1993). In addition, neuromagnetic investigation (Hari, Hamalainen, Illmonniemi, Kaukorante, Reinikainen, Salminen, Alho, Näätänen and Sams, 1984 and Csèpe, Pantev, Hoke, Hampson and Ross, 1992), while confirming the contribution of the supratemporal source to the MMF (mismatch field[97]) has failed to reveal sources outside of the supratemporal cortex (Sams et al., 1991)[98] [99] [100].

3.11 (C) THE PARIETAL MMN COMPONENT

In addition to the supratemporal and frontal components, there appears to be a right-hemisphere parietal component of the MMN. This is thought to reflect global auditory change detection (i.e., reflecting the activation of polysensory parietal areas which receive convergent acoustic, visual and somatic input and are thought to be less affected by the physical attributes of the stimuli than by their significance, Levanen and Sams, 1997).

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[97] (the neuromagnetic counterpart of the MMN).

[98] This may however be because magnetic recordings are sensitive only to the tangential components of the response, Sams et al., (1991).

[99] Alho et al (1994) found an attenuated MMN over a lesioned hemisphere in individuals with unilateral lesions of the dorsolateral frontal cortex; consistent with the possible involvement of a frontal cortex MMN generator or by diminished input from the lesioned frontal cortex to ipsilateral auditory cortex. Sustaining input from the frontal cortex is possibly needed for a proper functioning of the auditory-cortex mechanism underlying the MMN. Another explanation is that the auditory cortex MMN is first generated by a mismatch in the sensory-memory comparison process, which then activates the afore-mentioned frontal attention switch mechanism generating the frontal MMN subcomponent.

[100] Giard et al also suggests that the frontal MMN mechanism might in turn feed back to the auditory cortex and further augment the auditory cortex MMN. According to Näätänen and Alho (1995) the functional significance of such a fronto-temporal feedback process might be to facilitate the auditory cortex to detect any further changes or other relevant events in the sound source where the stimulus change eliciting the MMN occurred.

3.12 FACTORS AFFECTING THE ELICITATION OF MMN

MMN is elicited only when a change in stimulus sequence occurs. It is not affected by stimulus significance[101] (Näätänen et al., 1978) and is not elicited when a sequence begins or when stimuli are presented with long ISIs (Sams, Hamalainen et al., 1985). Shorter ISIs give MMNs of larger amplitude, longer duration and lower thresholds of elicitation[102]. In general, the larger the standard-deviant difference, the larger and earlier the MMN will be for the deviant stimulus (Näätänen, 1992). The MMN amplitude may saturate at a moderate magnitude of stimulus deviation (Novak et al., 1990).

In addition, the more infrequently the deviant tones appear in a sequence, the larger the MMN (Pekkonen, 1995). Näätänen et al. (1983) found a much larger MMN when the probability of deviant stimuli was 2% than when it was 10%[103]. However, this relationship appears to be dependent only upon stimuli occurring during the preceding 5-10 seconds (Sams et al., 1983, 1984); the global probability having no independent influence beyond that micro-sequence (Näätänen and Picton, 1986). For a greater review of such effects on the elicitation of MMN see Näätänen (1992) and Sinkkonen, Kaski, Huotilainen, Ilmonniemi, Näätänen and Kaila (1996).

3.13 THE ATTENTIONAL INDEPENDENCE OF MMN

Although MMN is generally accepted to be a reflection of the automatic and early stages of the extraction of auditory information, there is debate as to whether, under certain circumstances the MMN component may be modulated by attention, and therefore whether such early auditory processing may in fact be affected by attention under some circumstances.

According to Näätänen and Gaillard (1983), the MMN is unaffected by attention and therefore reflects the operation of a strongly automatic pre-conscious change-detection mechanism. According to Näätänen (1985), the apparent insensitivity of the MMN to attentional manipulation suggests that the neuronal traces underlying MMN generation encode physical stimulus features to an equally elaborated degree both for attended and unattended stimuli. This would suggest that the information obtained by

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[101] In testing this prediction attention paid to the stimulus sequence was controlled for, in order not to confuse the effects of attention and stimulus significance by presenting significant (target) and insignificant (non-target) deviants in random order in the same attended stimulus block.
[102] Näätänen, Teder, Alho and Lavikainen (1992) found a clear MMN with a constant onset to onset ISI of 60 msec when they were trying to determine the shortest ISI at which the MMN can still be elicited.
[103] In most MMN studies the probability of the deviant tones in the stimulus sequence is generally 10-20% (Lang et al., 1995).

the brain about the sensory features of an auditory stimulus is not weakened or made less accurate by withdrawing attention from it[104].

The original evidence for the attentional independence of MMN was based predominantly on data obtained from 'oddball' studies where participants are presented with a sequence of standard stimuli, irregularly interspersed by physically deviant stimuli. Under such conditions, the deviant stimuli were found to elicit an MMN even when the subject was not attending to the auditory input in which they were embedded, for example when the participant was reading (Näätänen et al., 1982; Sams, Paavilainen, Alho and Näätänen, 1985b; Paavilainen, Alho, Reinikainen, Sams and Näätänen, 1991) or attending to the opposite ear input in dichotic conditions (Näätänen, Gaillard and Mantysalo 1978, 1980; Alho, Paavilainen, Reinikainen, Sams and Näätänen, 1989). The negative difference waves obtained by subtracting the ERP for standard stimuli from those of deviant stimuli were found to be very similar for the attended and ignored output, indicating, according to Näätänen and colleagues, that MMN was independent of attention.

However Woldorff and Hillyard (1990) and Woldorff, Hackley and Hillyard (1991) criticised the type of studies performed by Näätänen and colleagues and their interpretation of the results. According to Woldorff and colleagues the slow stimulus-presentation rates used in Näätänen and colleagues' studies were not conducive for producing a strong selective focusing of attention. This could have resulted in attention being directed to the supposed non-attended stimuli, therefore enabling the monitoring of both relevant and irrelevant stimulus sequences for a change. Such monitoring would not therefore result in a strict independence of attention[105].

Subsequent studies looking at the attentional independence of MMN employed high-load dichotic studies with an instruction to attend to the designated ear and to ignore the concurrent input to the opposite ear (representing a stronger test to ensure attention has been withdrawn from a stimulus). Such studies have still yielded equal amplitudes for MMNs elicited by occasional frequency changes in the attended and unattended inputs (Alho et al., 1989; Näätänen, Paavilainen, Tiitinen, Jiang and Alho, 1993c; Paavilainen, Tiitinen and Näätänen, 1993). That such studies were not contaminated by attention switches to supposed non-attended input, Duncan and Kaye (1985 and Lyytinen et al, 1987 for example) was indicated by the elicitation of the MMN in the non attended channel without an accompanying P3a. For a review of such studies see Näätänen (1992).

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[104] Negativity indicates an increase in processing by the cerebral cortex. As illustrated by MNN it is very interesting therefore that there is an increase in negativity even though the participants were not attending to anything.

[105] (in fact some early research such as Sams et al., 1984 resulted in the elicitation of a P3a thought to reflect a transitory switch to irrelevant stimulus deviation).

It appeared therefore that task-irrelevant oddball stimulation elicits MMN even when the individual is performing a highly demanding primary task. In addition Alho et al., (1989) found that MMN was not affected by a considerable variation in task difficulty, which should affect the strength of the attentional focus.

3.14 ADDITIONAL EVIDENCE FOR THE ATTENTIONAL INDEPENDENCE OF THE MMN

Additional indication of the attentional independence of the MMN came from Scherg, Vajsar and Picton (1989). They suggested that if the MMN process were indeed an automatic, pre -attentive , pre-conscious brain event as originally proposed by Näätänen (1978) then it should not be affected by whether or not the participant can predict when deviant stimuli will be presented. This is indeed what Scherg et al. (1989) found, i.e., that predictability had no significant effect on MMN.

Recordings from cats (Csèpe et al., 1989) and Guinea pigs (Kraus et al., 1994a,b.) provided evidence for the occurrence of MMN without attention, i.e., during sleep and anaesthesia. In addition, Kane, Curry, Butler and Cummins (1993) demonstrated the emergence of a well defined MMN in coma patients and in addition found that that only those coma patients who regained consciousness one to two days later elicited this MMN. In those coma patients who did not regain consciousness there was an absence of MMN.

A MMN in ignore conditions has also been found to occur with no concomitant autonomic nervous system (ANS) response by Lyytinen and Näätänen, (1987), who suggested that this was further evidence of MMN elicitation in the absence of attention. It appears therefore that MMN can occur even without the participant consciously discriminating the stimulus that elicits the MMN. A MMN to undetected stimuli, i.e., a subliminal MMN, has also been reported (Näätänen and Gaillard, 1983). This MMN was of about the same magnitude as that for correct detections and 'not sure' responses. In contrast, the late positivity was only elicited by detected deviants and not sures. According to Näätänen (1992) this indicated that the MMN generator process does not underlie conscious discrimination and in contrast to P3 and other late responses, does not belong to its sequelae. Näätänen (1992) interpreted such results as indicating that MMN is generated by an automatic cerebral process that is a necessary, but not a sufficient condition for the conscious perception of stimulus change.

Näätänen et. al., (1987b) also found a MMN to frequency deviants even when the ISI (from onset to onset) was as short as 51 msec (stimulus duration 25 msec) and deviants occurring with a probability of 10%. Thus there were 20 discriminations to be performed every second, certainly too many for controlled (voluntary) processing, according to Näätänen (1990).

In studies using deviant tones which simultaneously differ from the standard on two features such as duration and intensity (e.g. Kurtberg et al., 1995) the MMNs that were elicited were larger than when deviants differed from standards on only one of the features. The latency of this MMN was however similar to that observed when the MMNs from each of the deviating features are elicited separately. According to Ritter et al., 1995, this suggests that the two features were processed in parallel, which is consistent with the view that the MMN is usually associated with pre-attentive automatic processes (Ritter et al., 1995).

Also, as the MMN occurs very early in stimulus processing, (considering the time from stimulation to arrival at the auditory cortex is about 12 msec), the onset of MMN around 40 msec after the earliest possible moment when the deviant could be detected indicates that discrimination was accomplished very early in stimulus processing, Ritter et al (1995)

3.15 SLEEP AND MMN; (Further evidence for the attentional independence of MMN).

Campbell, Bell and Bastien (1991); Alho, Sajanniemi, Reinikainen and Näätänen (1990); Cheour-Luhtanen, Alho, Kujala, Saino, Reinikainen, Renlund, Aaltonen, Eerola and Näätänen (1995) found evidence that MMN could be elicited during sleep, which according to these researchers provided further evidence for the attentional independence of MMN.

However, there has been inconsistency in the results of sleep-related studies of MMN. For example as Sallinen and Lyytinen (1997) report, MMN was found to be markedly attenuated (a) in sleepiness even when the optimal stimulus conditions for the MMN elicitation are used, (b) in sleepiness regardless of whether sleepiness is defined objectively or subjectively, and (c) in sleepiness that is characterised by severely impaired voluntary behavioural responding. According to Sallinen and Lyytinen (1997), this data suggested that the MMN can be affected by sleepiness, and indicated therefore that MMN may not be completely attention-independent.

However, the sleep-related attenuation of MMN may not necessarily mean that it is not independent of attention. Several other explanations can be found for the attenuation of the MMN during sleep. For example, the behavioural data in Sallinen and Lyytinen's (1997) study indicated that the decline of the MMN during sleepiness was accompanied by a markedly impaired awareness of the external environment. It is not, however, self evident that this phenomenon is responsible for the attenuation of the MMN. Although conscious awareness of the external environment is attenuated during sleepiness, the degree of general cortical activation decreases as well. Paavilainen et al., (1987) had already suggested that the latter phenomenon may be a more probable reason than the former for the failure to detect an MMN during sleep.

According to Winter et al. (1995) and Lang et al. (1995), changes in stimulus processing associated with the wake-sleep transition could also explain the attenuation of the MMN in sleepiness. Winter et al. (1995) argued that a totally different system is responsible for the processing of stimuli during sleep than during wakefulness and that this transition from the waking system to the sleep system occurs in sleepiness. The decay of the MMN may be characteristic of the sleep system because the activation of the brain processes reflected in the MMN threatens sleep continuity. Lang et al. (1995) proposed that the MMN latency starts to fluctuate strongly during the wake/sleep transition which could result in a reduction in the averaged MMN even though single trial MMNs may not vary.

In view of the apparent insensitivity of the MMN to attentional manipulation, Näätänen and colleagues proposed that the neuronal traces underlying MMN generation encode physical stimulus features to an equally elaborated degree both for attended and unattended stimuli. This suggests, according to Näätänen (1990), that the physical stimulus features represented in the traces must have been analysed to the same extent by the sensory systems in both cases, thus supporting the late selection view. Näätänen (1990), suggested that such a sensitive response to deviation, in an unattended input would have been impossible unless the neural traces underlying MMN generation had not contained fully processed sensory information (Näätänen, 1990).

Näätänen, (1990) proposed therefore that all the physical features of auditory stimuli receive a rapid and complete analysis by means of a hard-wired, strongly automatic, pre-attentive mechanism with no efferent or top-down control of this processing, which therefore provides the brain with sensory information of the same quality irrespective of the direction of attention.

3.16 EVIDENCE FOR HOW THE MMN MAY BE AFFECTED BY ATTENTION.

However, a challenge to the notion that the MMN is not affected by attention was advanced by Woldorff et al. (1991).

Woldorff et al. (1991), performed a study with very highly focused attention conditions and found that the MMN to occasional decrements in stimulus intensity occurring in an unattended auditory input was attenuated in amplitude compared to when it was attended. In this study, a very difficult task was used (the conditions were optimal for developing a sharp attentional focus, i.e., short ISIs, and widely different and thus easily separable relevant and irrelevant channels and a difficult within-channel task).

Woldorff et al. (1991) suggested therefore that the MMN can be affected by very strongly focused attention and interpreted the amplitude reduction of the intensity MMN caused by the withdrawal of attention, in terms of attenuated sensory processing in unattended channels. Woldorff et al. suggested

therefore that the MMN may only be weakly automatic, i.e., not totally independent of attentional influence.

However, Woldorff et als' interpretation of the results was questioned by Näätänen, (1991), who suggested that the scalp distribution of the attentional enhancement found in Woldorff et. als.' deviant-standard difference suggested instead a major contribution of the N2b component in the attended channel. Näätänen suggested that the N2b component was summed with the MMN in the attended-input data, therefore failing to permit a separate measurement of the MMN component in the attended input and therefore accounting for most of the MMN attention effect.

Further studies by Näätänen, (1991) and Näätänen et al., (1993) that disentangled the contributions of the MMN and N2b components, indicated that although the MMN to frequency change cannot be eliminated even by very efficient withdrawal of attention, the withdrawal of attention from intensity change results in reduction of intensity MMN amplitude.

However, Näätänen (1993) results concerning attention effects on frequency and intensity MMNs were in fact confounded, as the intensity deviants proved to be much more difficult to discriminate than the frequency deviants, therefore confounding the effects of the deviance type and discriminability. As reported by Paavilainen et al (1993), if it had been more difficult to discriminate pitch than intensity changes, then one might have got opposite results, ones suggesting that the attention dependence of the frequency MMN but not of the intensity MMN.

Other studies also supported the attentional independence of frequency analysis, for example, Näätänen, 1990, 1991, 1992; Alho et al., (1989); Alho, Woods, Algazi and Näätänen, 1992; Paavilainen et al., 1993.

To explain this differential sensitivity of the frequency and the intensity MMNs toward attentional manipulation several ideas have been proposed.

One suggestion is that the processes responsible for encoding and/or storing frequency and intensity information could be differentially modulated by attention[106] with attention having different consequences for different features.

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[106] A proposal that finds some support from Woldorff and Hillyard's (1991) suggestion that attention may be able to affect auditory processing at early stages of processing, together with evidence that attention may affect auditory processing at the level of the cochlea (Giard et al 1994; see however Michie et al, 1996). See also Shröger (1997).

Näätänen et al. (1993), argued however that it is the MMN generator process (more specifically, the amplification of the initial mismatch signal) rather than the antecedent sensory analysis and storing functions that is dependent on attention. Näätänen, (1991) suggested that two types of neuronal populations might be involved in MMN generation,: (1) The *computational* (informational) neurons and (2) the *amplifying* (modulating) neurons, of which only one could be liable to attentional influences.

The computational neurons are characterised as being highly stimulus-specific and specialised to respond even to the slightest stimulus deviations. These neurons were proposed by Näätänen to be fully independent of attention and to generate the 'mismatch signal' for the amplifying neurons which receive and amplify the initially weak signal originating from the computational neurons. The amplifying (modulating) neurons could however, according to Näätänen, be affected by attention.

Näätänen (1995) suggested that both types of neurons might exist in the supratemporal cortex and contribute to the supratemporal subcomponent of the MMN. The amplifying system could account for vigilance and drug effects on MMN[107] (see Näätänen 1992). Stimulus changes detected in this automatic analysis may not as easily pass into consciousness in the absence of attention as when attention is present (Näätänen, 1991, 1992).

According to Näätänen (1995) the same amount of information extracted from stimulus deviation by the computational mechanism might result in MMNs of different sizes because of the different excitability of the amplifying system. This distinction could therefore explain an attention effect on the MMN amplitude without an effect on the MMN occurrence (i.e., the threshold of MMN elicitation). This pattern of results would be obtained if the computational system is not affected by attention but the amplifying system is. In this case, sensory information would be fully processed even in the absence of attention, whereas the assumed alarming, attention switching function of the MMN system might then be dampened because of the attenuated amplification of the mismatch signal generated by the computational system.

It would be difficult to explain how the basic processing, i.e., that leading to the development of initial stimulus representations of one but not of another basic attribute of the same auditory stimulus could be modulated by attention. Thus the attentional insensitivity of the frequency MMN elicitation threshold apparently rules out the present intensity-MMN data as evidence for attentional suppression of the afferent sensory inflow in the unattended channel. The attenuation of the intensity MMN in the absence of attention is consequently, probably due to the attentional dependence of the MMN generator process

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[107] In particular Born et al (1987a, 1987b; Born, Fehm-Wolfsdorf, Lutzenberger, Voigt and Fehm, (1986) and Born, Kern, Fehm-Wolsdorf and Fehm, (1987c) have found MMN-amplitude enhancement after intake of arousing drugs and attenuation with sedative drugs.

itself (its amplifying system) rather than to that of the antecedent sensory analysis and storing functions (Näätänen 1995).

To take account of the attention-modulation debate, Hackley (1993) has described MMN as 'obligatory but subject to attentional modulation'. According to Näätänen, (1995) however, the degree of attention independence of the MMN is sufficient to justify its use as an objective measure of sensory analysis in audition

3.17 THE CLINICAL IMPORTANCE OF AUDITORY MMN

One of the major advantages of using the auditory MMN to assess auditory function compared to other event related potentials is that those associated with active cognitive processes are highly variable and are sensitive to fluctuations in attention whereas, as described in the above sections, MMN is a predominantly automatic response that is not significantly influenced by attention (except under certain conditions, Kurtzberg et al. 1995).

The auditory MMN technique also has the ability to assess discriminative capabilities in individuals whose auditory capacities are difficult to determine, including young children, older adults and individuals with severe cognitive impairment, (Kurtzberg, Vaughan, Kreuzer and Fliegler 1995), where conventional techniques are not appropriate, or possible to apply.

Mismatch negativity measurement has already been applied to the differentiation of several brain-related pathological processes, with encouraging results, which may lead to its use in the differential diagnosis of such disorders and the monitoring of disease progression. Examples of auditory MMN in clinical application include the study of Schizophrenia (where several studies have indicated reduced MMNs in schizophrenia e.g. Shelley et al., 1991; Oades 1991, Javitt et al., 1993; see also Javitt, Doneshka, Grochowski and Ritter, 1995); hearing rehabilitation after cochlear implant (Ponton and Don, 1995) and coma patient prognosis (Kane, Curry, Butler and Cummins 1993). The MMN has also been applied to the estimation of individual auditory capacities, with Lang et al., (1990) for example finding a strong relationship between the individual behavioural pitch discrimination accuracy and the MMN amplitude for changes in tonal frequency recorded in passive conditions.

Of importance in the area of potential clinical use was the finding that the MMN has good replicability, not only at the group but at the individual level[108] (Pekkonen, Rinne and Näätänen, 1995).

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[108] (although a large number of stimuli must be used in order to obtain individual level data to improve the signal to noise ratio and therefore increasing its clinical applicability).

Of particular importance to the present study are the results of previous studies investigating the effect of Alzheimer's disease and ageing on auditory MMN.

3.18 AUDITORY MISMATCH NEGATIVITY AND ALZHEIMER'S DISEASE

Previous studies evaluating auditory stimulus processing using auditory mismatch negativity in AD have been performed in order to determine whether such measurements can provide information regarding the differential diagnosis of AD from ageing, other types of dementia and other neurological disorders. Although none of these studies have provided a definitive peripheral marker for the presence of AD or other neurological disorders at the individual level, they have provided additional potentially useful diagnostic and theoretical information.

Verleger, Kompf and Neukater (1992) measured auditory MMN in seven individuals with AD, (using an active oddball paradigm) and found that MMN was about the same in AD patients as in age matched healthy controls in the 90-160msec latency range[109]. Although the MMN component appeared to be 'normal' in AD compared to age matched controls, Verleger et al (1992) did however find that the auditory N2 was delayed and that this delay was specifically due to a delay of its N2b component. As it is generally agreed that the N2b reflects a conscious controlled stage of processing (Näätänen 1986) and might reflect the decision on how to respond to a stimulus, such a finding could indicate that, after having correctly noticed the mismatch (as reflected by the MMN) the individuals with AD were impaired in deciding on the consequence, as reflected by their delayed (and in some cases also reduced) N2b. It appears therefore that in AD, stimuli are detected in the normal way by early auditory processing but are abnormally processed by later auditory processes. In other words, automatic (pre-attentive) auditory processing appears to be preserved in AD, while later, attention-related processing is detrimentally affected.

Pekkonen, Jousmaki, Kononen, Reinikainen and Partanen (1994), also indicated however, that MMN was more attenuated in individuals with AD than age-matched controls as a function of ISI. Although their results suggested that automatic stimulus-change detection is not impaired in AD (in agreement with Verleger et al, 1992), when short ISI (i.e. 1sec) are used, (indicating that the MMN generators are not affected per se), when longer ISIs (3 sec) are used, the mechanism used to store stimulus information appears to be impaired in AD. The MMN amplitude decreased as a function of the ISI more in the AD group than in the control group, suggesting that the memory trace decays faster in AD than in age-matched controls (Pekkonen et al. 1994). This finding is interpreted as a failure of echoic memory caused by degenerative changes in the temporal cortex in AD.

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[109] Because an active oddball paradigm was employed, the N2b component partly overlapped the MMN, so to avoid this overlap, the authors used the early time window of 90-160 msec to measure the MMN.

3.19 AUDITORY MISMATCH NEGATIVITY AND AGEING

The results of a study by Pekkonen, Jousmäki, Partanen and Karhu (1993), indicated that MMN to duration and frequency change was stable regardless of age with short ISIs (i.e., 1 sec). Such a finding, according to the authors indicates that automatic stimulus change detection per se is not impaired in normal ageing[110]. Pekkonen et al., (1993), did however find evidence that the memory trace decays faster or involuntary attention switching is less sensitive, with ageing and also that the recovery period of neurons generating N100, which contributes to stimulus detection, seems to be lengthened with ageing. In addition, with a 3sec ISI (as opposed to 1sec ISI) MMN was significantly smaller in old compared to young adults and may reflect the shortening of sensory memory trace with increasing age.

Lang et al (1995, cited in Näätänen 1992), conducted a study of age effects on MMN to a frequency change recorded in a passive situation. No age effect was found for the MMN, whereas the P3 latency (see Bashore 1990, for a review) was systematically prolonged with age in a separate active oddball condition in the same subjects. They were therefore able to conclude that the P3-latency increase with ageing was not due to age effects on the automatic discrimination process that generates MMN but rather to age effects on some later process (of perceptual-cognitive nature, judging from the fact that the P3 latency does not reflect response-related processes).

In both 'normal ageing' and AD therefore, early auditory processing appears to be relatively preserved compared to the later attention-related processing. An interesting contrast to this pattern of results has been found when measuring auditory MMN in Parkinson's disease; a neurodegenerative disorder that affects different parts of the brain to AD. It is the finding of such dissociations that could point to the use of mismatch negativity in the differential diagnosis of different types of dementia.

3.20 AUDITORY MISMATCH NEGATIVITY AND PARKINSON'S DISEASE

Studies by Stam, Visser, Op de Coul et al (1993) and Pekkonen, Jousmaki, Reinikainen and Partanen (1995), suggest that automatic stimulus -change detection, indicated by MMN, is impaired in PD

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[110] As described by Pekkonen (1995) this finding contrasts with the results of Czigler et al (1992) and Woods (1992), but at least two reasons might explain to some extent the differences. In both studies by Pekkonen et al, stimulus loudness was adjusted according to the subjective hearing level to minimise age-related changes of hearing. Czigler, however, used constant stimulus loudness irrespective of the participant's age. The ability of the inner ear to transform acoustic waves into electrical signals impairs in normal ageing. Therefore , the same stimulus loudness presented to all participants irrespective of their age might alter cortical ERP responses due to peripheral reasons. In Woods' study, the subjective hearing level was measured. Tones were however, presented binaurally and, in addition, their deviant tones were longer in duration than the standard tones.

patients. They found that MMN was significantly smaller in PD than in age-matched controls, suggesting that PD patients have impaired stimulus change detection compared with healthy controls. This represents a dissociation of results with those found for AD. The authors also found that in the attended condition, the amplitudes of both N1 and N2 complex were smaller in PD than in controls.

Although, their results indicated that a single MMN measurement cannot as yet distinguish a PD patient from a healthy control at the individual level, MMN may be useful as a tool for following up signal processing in PD. Pekkonen (1995) also points out that as some individuals with PD eventually develop dementia (Adams and Victor 1989), an interesting question is whether MMN attenuation precedes the appearance of dementia symptoms in PD patients.

3.21 THE EFFECTS OF DRUGS ON AUDITORY MMN

Several studies have indicated that MMN may be enhanced by drugs that have a general activating effect on the CNS and attenuated by drugs with deactivating effects. For example, Born, Bother et al., (1987) and Born, Fehm-Wolfsdorf, Lutzenberger, Voigt and Fehm, (1986) found that the MMN amplitude for frequency deviation was enhanced by lysine-vasopressin (LVP) which belongs to a group of pituitary-hypothalamic hormones known to enhance cortical arousal (Timsit-Berthierr, Mantanus and Legros 1983). In another study, hydrocortisone substantially reduced the MMN amplitude for frequency deviants (Born, Bruninger et al 1987). The N1 amplitude was also reduced by hydrocortisone. The authors suggested that glucocorticoids not only lower stimulus induced arousal N1, but also diminish sensitivity to stimulus change MMN.

The sensitivity of the auditory MMN to certain drugs may, with future studies, provide an indication of the effects certain drugs may have on the brain and may in addition, have the potential to indicate the effectiveness of certain drugs used in clinical trials.

3.22 THE EFECTS OF ALCOHOL ON MMN

Alcohol-induced attenuation of the auditory N1 and P2 amplitudes has been consistently reported (see for example Campbell and Lowick, 1987; Gross, Begleiter, Tobin and Kissin, 1966; Hari, Sams and Jarviillehto, 1979; Teo and Ferguson, 1986). A recent study has found suppression of the MMN to unattended 10% changes in tone frequency with a blood alcohol concentration of 0.5-0.6% (Jaaskelainen et al., in press, cited in Jaaskelainen et al., 1996). The ethanol-induced disturbance did not appear to involve the automatic process for detecting change (reflected supratemporally) nor the auditory sensory

memory trace which it uses, but rather the mechanism thought to lead to an attention switch triggered by the earlier pre-perceptual change detection in the auditory cortex (Jaaskelainen et al 1996).

3.23 THE SEARCH FOR A VISUAL ANALOGUE OF AUDITORY MMN

The great potential applicability of the auditory MMN for the measurement of brain function in neurological disorders and how certain drugs and alcohol can affect brain function, has prompted the present search for its visual analogue. If such a visual event-related potential does exist it could not only have great potential for the study of visual processing in general, but also for the measurement of such processing in ageing, AD and other neurological disorders.

The following sections will provide an overview of some of the theoretical arguments surrounding the existence of a visual analogue of the auditory MMN and some of the previous methods used for its elicitation.

3.24 THE QUESTION OF WHETHER A VISUAL ANALOGUE OF THE AUDITORY MISMATCH NEGATIVITY EXISTS.

Although Näätänen (1992) has argued that it is of vital biological significance that pathways of early sensory processing are not inhibited or blocked by the withdrawal of attention, and that the automatic processing of change in the environment is of great biological significance in the shifting of attention to that change, he proposed that a visual analogue of the auditory MMN does not exist. However, if the auditory MMN reflects the automatic processing of the physical attributes of auditory stimuli and plays a part in directing attention to stimuli of biological importance (such as deviations) then one would expect a similar mechanism to be in place for the visual modality and indeed for the other sensory systems.

Näätänen (1990) argued against the existence of a visual mismatch negativity on the grounds that whereas auditory processing is serial in nature, visual processing is largely parallel; suggesting that MMN reflects only changes in sequential/serial processing. In addition, Näätänen argued that the lack of a visual analogue of the auditory echoic memory also precluded the elicitation of a visual MMN.

Although the neurophysiological basis of such a process may not be the same, there is evidence however for the existence of 'deviance' detectors within early or automatic visual processing together with the existence of visual neural traces.

In visual search tasks, (where a pre-defined target has to be detected in a field of distractor stimuli), when the target and distractors differ on a highly discriminable dimension, attention is very rapidly and automatically directed to the spatial location of the target; the target is therefore detected and identified rapidly and is said to 'pop-out' (Treisman and Gelade 1980). For this non-sequential detection of deviance, one assumes that the neural traces or representations of the deviant, (i.e., target) and the standard (i.e., or distractor) stimuli are produced in parallel and consequently compared in parallel, resulting in some kind of mismatch signal (see Duncan and Humphries 1989[111] and Sagi and Julesz 1984[112]).

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[111] Duncan and Humphries (1989) suggested that pop-out is a mechanism by which attention is automatically directed to a deviant stimulus in a parallel visual scene and is thought to occur in response to a local mismatch detection strategy.

[112] According to Sagi and Julesz 1984, parallel visual processes include 'local mismatch detection'. With reference to a set of elementary stimulus features (for example wavelength, orientation, colour) each element in a visual field is compared in parallel to its immediate neighbours. Such a process could indicate where targets [or deviants] occur since they are the elements most unlike those immediately surrounding them. A subsequent attention-related process is then needed to determine why a mismatch has occurred (i.e., to identify the deviance).

It is not yet clear whether a MMN-like component is produced by such deviance in parallel automatic visual processing, but there is evidence that the deviance reflected by such stimuli is apparent in visual ERPs (see Luck and Hillyard 1994a).

Johnston, Hawley and Farnham, (1993) also describe the phenomenon of 'novel pop-out' in the visual system. This is described as a mechanism which ensures a degree of vigilance to environmental change, enabling noticing of 'the unexpected' in the environment, which Johnston et al., (1993), suggest can be accounted for by their so-called 'mismatch theory'. The general idea of their mismatch theory is that soon after exposure to a visual scene, the perceptual system becomes relatively unresponsive to stimuli that match expectations. In turn, this inhibition of perceptual activity for expected stimuli yields an increase in the perceptual activity for any unexpected stimulus in the scene (see also Watson and Humphreys, 1997). Novel pop-out enables organisms to rapidly detect unanticipated intrusions into their habitats. Johnston et al (1993) describe the shift of attention to novel stimuli as a natural by-product of inhibitory and disinhibitory processes operating locally.

One must remember also that sequential as well as spatially parallel visual processing occurs. Perceptual phenomena such as temporal integration and retroactive masking shows that the visual system handles incoming information in a temporally distributed manner. There are numerous changes in a visual scene over time and the visual system therefore requires some mechanism to detect them. It is this type of 'sequential' change detection in the visual system that may more closely resemble the elicitation of auditory MMN. Of course there may be several different mechanisms that underlie deviance detection in vision, depending on whether the deviance occurs in space or time.

Näätänen (1990) however, claimed that another reason why a visual analogue of the auditory MMN would not exist was because the visual analogue of echoic memory; iconic memory (see Neisser 1967) does not last long enough for a comparison process between standard or (common) visual stimuli and deviants, being less than 0.5 seconds in duration.

However as Phillips (1983 in Haber 1983) and Julesz (1983) suggested, the visual equivalent of the auditory echoic memory is not the iconic memory but another longer form of short term visual memory. Greenlee, Koessler, Cornelissen and Mergner (1997), in a fMRI and PET study, also found evidence for the existence of distributed visual memory systems in the human neocortex. So Näätänen's assumption about visual mismatch negativity and iconic memory may be misplaced as the comparitor system could exist in a different form of visual memory. (See also Jonides, Smith, Koeppe, Awh, Minoshima and Mintun, 1993).

Desimone and Duncan (1995) also describe the existence of numerous short term memory mechanisms in the visual system and describe how, for some cells in the visual system, suppression occurs when a stimulus has recently been seen, whereas enhancement occurs for other cells when the current stimulus

matches the memory trace of a specific stimulus the animal holds in visual memory[113]. There appears therefore to be an automatic suppressive mechanism based on simple stimulus repetition and a voluntary enhancement mechanism linked to stimulus activity maintained in memory. Such mechanisms are thought to occur early in the visual system, particularly the inferior temporal cortex, V1 and V4.

However, as described in section 3.6 of the current chapter, there is still argument as to whether the auditory MMN is dependent upon auditory echoic memory so Näätänen's discussion of a visual MMN in terms of visual memory may be inappropriate.

There has been relatively little research performed in an attempt to discover the existence of a visual analogue of the auditory MMN and the studies that have been performed have tended to be 'by-products' of the study of visual spatial selective attention rather than studies aimed specifically at determining the existence of a visual analogue of the auditory MMN.

The following sections will describe some of the evidence surrounding the visual MMN debate in terms of the research performed on visual selective attention.

3.25 ELECTROPHYSIOLOGY AND VISUAL SPATIAL ATTENTION

As with auditory attention there has been a long standing debate about the level of processing at which visual attention operates. This debate has predominantly taken the form of attempting to determine the level to which visual information can be processed independently of spatial attention, i.e., automatically.

ERP recordings have been used to address the level-of-selection issue for visuospatial attention in a manner analogous to the auditory attention studies described previously. Several studies have indicated that visual stimuli presented within the focus of attention produce enhanced sensory (exogenous) evoked P1 (80-120 msec) and N1 (140-190 msec) components relative to unattended stimuli, (Heinze, Luck, Mangun and Hillyard (1990); Luck, Heinze, Mangun and Hillyard (1990); see Näätänen, (1992); Hillyard, Mangun, Woldorff and Luck, (1995), for reviews).

According to Mangun and Hillyard (1990) the P1 and N1 'attention-effect' occurs in the extrastriate visual cortex as opposed to the striate cortex (see also Mangun et al., 1993). That the 'attention-enhancement effect occurs at the level of the extrastriate as opposed to striate cortex has also been supported by evidence from single unit recordings in monkeys which have demonstrated attention-sensitive neurons only in extrastriate regions (see also section 2.23 -2.30 inclusive, in chapter two of this thesis). (See also Mangun, Hopfinger, Kussmaull, Fletcher and Heinze, 1997, for PET study evidence for the early attentional gain process acting in the extrastriate visual cortex).

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[113] These findings were found in monkeys using a delayed matching to sample task.

This characteristic ERP pattern has been interpreted as indicating the attentional modulation of early visual stimulus processing and thus evidence for early selection[114], (see; Hillyard, 1993; Hillyard, Mangun, Woldorff and Luck 1995 and Mangun, Hillyard and Luck; 1993, for reviews)[115].

The N2 is thought to belong to the family of negative ERP waves associated with stimulus evaluation and classification, (i.e. discriminative processing leading to target classification processes). The N2 is modality specific and associated with the detection of infrequent targets. Visual targets tend to elicit an N2 that is largest over occipito-temporal cortices.

The results of a study by Heinze et al. (1990), indicated that the visual N2[116] is only elicited when the stimulus occurs at the attended location. The absence of any significant elicitation of an N2 component at non-attended locations was interpreted by Heinze et al. (1990), as further evidence for an early selection mechanism whereby the lack of elicitation is due to the termination of further processing in unattended locations, suggesting that unattended items are filtered early and do not reach higher levels of processing.

There is however some evidence that non-attended visual stimuli can evoke N2 or N2-related waves. Thus suggesting, (as Näätänen proposed for the auditory system) that visual stimuli can be processed to a high level before being selected. For example, Ritter et al (1983) found that even irrelevant physical stimulus deviations may in some cases elicit an N2 wave and proposed therefore that this component reflected automatic as well as controlled stimulus classification processes. Wijers et al (1987) found that unattended target letters elicited a larger N2 deflection than did unattended non-targets and considered

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[114] I.e. that spatial attention produces a facilitation of the visual pathway that affects all stimuli within the focus of attention; consistent with early selection models of attentional processing. So the perceptual analysis of attended stimuli is facilitated relative to that of unattended ones.

[115] These early P1 and N1 changes appear to be unique to spatial attention and do not appear to occur during attention to non-spatial features. Attention to other visual stimulus features such as colour (Harter and Salmon, 1972; Hillyard and Munte, 1984; Hillyard, Munte and Neville, 1985; Wijers, Mulder, Okita, Mulder and Scheffers, 1989a), orientation (Harter and Guido, 1980; Rugg, Milner, Lines and Phalp, 1987) or spatial frequency (Harter and Previc, 1978; Previc and Harter, 1982) does not appear to enhance exogenous ERPs (i.e. there are no early P1/N1 amplitude modulations) and thus attention does not appear to affect their early processing (see however Zani and Proverbio 1997).

Early processing of these features appears therefore to be unaffected by attention and selection is instead predominately associated with later, slow negativities which appear to be very similar to the PN in auditory selective attention mentioned earlier. These negativities in the visual modality were termed selection negativities (SN) for example by Aine and Harter, (1984a, 1984b, 1986) and Harter and Anllo-Vento, (1990, 1991). So attention to non-spatial features is indexed by longer-latency ERP components in the 150-350 msec range that are largely endogenous (i.e. components triggered specifically by attended stimuli but not otherwise). It is plausible that these endogenous slow negativities associated with visual stimulus selection could be accounted for by a matching process similar to Näätänen's (1990;1992) attentional trace theory of auditory selective attention.

this as evidence for automatic letter classification outside the focus of attention. In addition, Drysdale, Finlay and Fulham (1995) also examined attended and unattended visual stimuli in visual selection using bilateral stimulus presentation and found evidence of N2 enhancement for unattended targets, i.e., a difference was found between target and non-target material presented at the unattended location.

If spatial attention is indeed required for the processing of stimuli at a specific location, then stimuli at unattended locations should not produce a visual MMN, i.e., an indicator of automatic sensory processing. The presence of a VMMN to stimuli presented outside the spatial focus of attention would however indicate that visual stimuli could be processed independently of spatial attention, i.e., be processed automatically. The finding of a visual analogue of the auditory mismatch negativity, to deviant visual stimuli outside the spatial focus of attention would therefore have potentially significant implications for current theories of spatial visual attention and the level of selection argument.

The occurrence of a visual MMN elicited in the absence of attention would indicate that the initial stimulus representation of visual stimuli is unaffected by the lack of attention because a sensitive response to a deviation in an unattended input would not be possible unless the neural traces underlying MMN generation had not contained fully processed sensory information. The elicitation of VMMN would therefore indicate that information obtained by the brain about the sensory features of a visual stimulus is not made less accurate or processed less by withdrawing spatial attention from it.

A strategy that eliminates entirely unattended stimuli would not appear to be very useful. Such a strategy would probably be unnecessarily wasteful of information that could potentially be ecologically and biologically useful, for example in controlling switches of attention. The advantage to the organism conferred by the MMN mechanism in the auditory modality would suggest therefore that similar mechanisms would exist in other modalities

[116] In visual discrimination tasks, the N2 is considered to be a correlate of stimulus categorisation (Ritter et al., 1983) and orientation to the stimulus (Renault et al., 1982; Czigler and Csibra, 1990).

3.26 THE RESULTS OF PREVIOUS STUDIES LOOKING AT THE EXISTENCE OF VISUAL MISMATCH NEGATIVITY

In the relatively few studies that have been performed in relation to visual mismatch negativity, none have elicited a component analogous to the auditory MMN, i.e., a component that is elicited by deviant stimuli embedded in a series of standard stimuli; independently of attention and stimulus significance or salience and which is modality specific and not confounded by target detection and response effects.

Previous studies incorporating visual MMN have used numerous different stimuli and experimental designs with varying methods of attentional manipulation which makes their comparison and interpretation difficult. Several electrophysiological studies have been performed in which visual N2 components have been elicited (Simson et al., 1977; Ritter et al., 1983), some of which have had several similarities with the auditory MMN. There has however been a failure to elicit a visual analogue of the auditory MMN that fulfils the criteria for the existence of the auditory MMN.

An essential characteristic of a mechanism for detecting novel or changed stimuli is that it must operate automatically if it is to detect potentially significant events that are not currently the focus of attention. Several previous claims for the existence of a visual MMN can be rejected on the grounds that the effects have not been evoked by unattended or irrelevant stimuli. For example:

Using repetitive visual stimuli, Ritter et al. (1983) reported an N2 to infrequent, irrelevant visual pattern changes, (i.e. Ritter reported an N2 to infrequent visual pattern changes, both when these changes were targets and when they were not). But because of the possible role of attention, their N2 to infrequent, irrelevant visual pattern changes cannot be interpreted in terms of a visual MMN (the participants pressed a button in response to all visual stimuli, Näätänen 1990).

In a study by Nyman et al (1990), there was some evidence for a difference in the ERP between the standard and deviant visual stimuli in the N2 range. However, these differences were confounded by changes in luminance between the standards and deviants and there was no attention-independent condition to determine whether an attentional independent sub-component (an analogue of the MMN) may exist.

Czigler and Csibra (1990; 1992) also reported a posterior N2 response evoked by infrequent stimuli in a shape discrimination task. Unlike auditory MMN however, it was evoked only when the deviants were attended and salient. Cammann (1990) found a widely distributed negative component evoked by a change in the colour of light emitting diodes which participants fixated while responding to auditory tones. The possibility that the fixated visual stimuli were covertly attended cannot however be excluded.

The strongest evidence for a visual MMN has been provided by two back-to-back studies of intermodal selective attention by Woods, Alho and Algazi (1992) and Alho, Woods, Algazi and Näätänen (1992). Visual deviants[117] evoked an early negative component (which they referred to as deviance-related negativity) when they were attended and also when attention was directed to the auditory modality. It was suggested by the authors that this negativity shared certain characteristics with the auditory MMN in that it originated in the lateral occipital and infero-temporal cortex of the hemisphere contralateral to the stimulated visual fields, consistent with generation in modality-specific sensory cortex and that because it could also be elicited when attending to the auditory modality, it was generated by a largely automatic discrimination process.

However, the phenomenon did not occur if the difference between unattended deviants and standards was small, unlike the auditory MMN which can be elicited by stimuli close to the discrimination threshold. Sams, Paavilainen, Alho and Näätänen, (1985) suggested therefore that a visual MMN may have a higher threshold for elicitation than the auditory MMN. Czigler and Csibra (1991) and Alho et al., (1992) also suggested that a visual MMN might be sensitive to changes in only certain stimulus features, unlike auditory MMN which can be evoked by any perceivable change in the physical properties of the sound (Näätänen, 1990). In addition, the deviance related negativity resembled the occipital negativity that occurred following visual targets presented alone. Consequently these studies may have been confounded by attention-related effects, in that attending to and performing a difficult auditory task may not have prevented some attention being employed to the supposedly unattended visual system.

Prechtl and Bullock (1993) looked for a visual MMN in the visual areas of the turtle brain. Changes in the turtle VEPs were found that could be attributed to the encoding of stimulus rarity or mismatch. Prechtl and Bullock referred to these potentials as mismatch potentials because they were derived with a mismatch paradigm and they correlated with change itself as opposed to any dimension of the deviant stimulus. The mismatch potentials were found to be generated by at least three regions. Their results indicated that mismatch responses could be recorded in the projection areas of visual pathways in the midbrain and forebrain[118]. However, Prechtl and Bullock did not manipulate attention or rule out its operation during the experiment and therefore could not exclude the possibility that the observed mismatch potentials share features with the attention-sensitive deviance-related negativity reported by Alho et al., (1992) after visual mismatch stimuli.

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[117] The standard or common visual stimuli consisted of serially presented vertical gratings. The deviants were of two sorts; either for easy discrimination, where the deviant was a lot shorter than the standards or for difficult discrimination, where the deviant was only slightly shorter than the standards and therefore more difficult to discrminate.

[118] (the existence of subcortical mismatch potentials caution against assigning a primary or exclusive role to those recorded from the cortex).

Luck and Hillyard (1994a) describe three N2 components with distinct topographical distributions (anterior N2, posterior contralateral N2pc and posterior bilateral N2pb) evoked by target stimuli (i.e. deviants) in a visual pop-out task. Both target and non-target pop-outs elicited an enhanced (more negative) anterior N2 component. The finding that the anterior N2 may be elicited by both targets and non-targets suggests that it may be related to the auditory MMN. The participants were not however strongly motivated to ignore the non-target pop-outs and therefore the associated N2 cannot be considered as being strictly automatic in nature. Also, when the participants were told to ignore the pop-out stimuli and to respond only to the colours of the array the anterior negative enhancement was eliminated. So although the deviant or pop-out stimuli were present they did not produce a negative enhancement of the N2.

Thus deviance-related negativities, such as visual N2, N2-subcomponents and MMN-like components have been demonstrated in the visual modality in a number of different paradigms, which indicates that there may be some support for a visual MMN. However, it appears that many of these effects are not homologous with auditory MMN, particularly where they do not occur in the absence of attention to the stimuli (Näätänen 1990, 1992; Näätänen and Gaillard, 1983). So a visual analogue of auditory MMN has not been clearly demonstrated, but related visual potentials that are sensitive to attention have been found and are known as deviance-related negativities.

The failure to elicit a visual MMN may be the result of not having an appropriate visual experimental design and as the major criticism of the previous studies has been predominantly in the form of lack of automaticity, a study was required which tried to ensure that attention was successfully drawn away from standards and deviants. If a MMN-like visual component could still be elicited in the absence of attention then it may be judged more favourably as corresponding to a visual analogue of the auditory MMN.

The following experimental section will describe the series of studies performed in an attempt to elicit a visual analogue of the auditory mismatch negativity. Several types of visual stimuli were employed in an attempt to determine the most appropriate for the elicitation of a visual mismatch negativity. In addition, attention was manipulated in an attempt to produce an experimental design in which attention was maximally directed away from the stimuli designed to elicit the visual MMN thus reducing the confounding effects of attention on the results.

If a visual analogue of the auditory mismatch negativity is elicited by these studies, the VMMN elicited by the younger adults will be compared to that elicited in older adults. In addition, the VMMN in older adults will be compared with that in older adults with Alzheimer's disease.

3.27 EXPERIMENTAL SECTION

That a visual mismatch negativity can be elicited independently of spatial attention is of paramount importance in terms of its definition, i.e., as a 'true' analogue of auditory MMN. The experimental strategy was therefore aimed at presenting both the standard and deviant stimuli to a location outside of the focus of attention and maintaining fixation and attention away from that location.

3.27 (a) PILOT STUDY ONE

The first study was based on a technique used by Hillyard and colleagues (e.g., Hackley, Woldorff and Hillyard, 1990; Mangun and Hillyard 1988) to determine whether attending to a stimulus compared to not attending to it, enhanced its associated ERP components. The design employed bilateral stimulus presentation where stimuli were flashed one at a time in a rapid sequence to the left and right visual field locations in a randomised order. Participants maintained fixation on a central point while attending exclusively to the stimuli on one side at a time. The task was to detect and respond to infrequent target stimuli embedded in the stream of stimuli at that location; the stimuli that occurred on the other side were to be ignored.

This technique provided a situation in vision that was analogous to that in the dichotic listening studies used in the elicitation of auditory mismatch negativity[119]. It represented a way in which the ERP responses to a series of non-attended standard and deviant visual stimuli could be measured in order to determine whether a visual analogue of the auditory MMN could be evoked.

In the present study the sequence of stimuli at both attended and unattended visual spatial locations consisted of a train of standard stimuli interspersed with rare stimuli. In the attended location, the rare stimuli, (deviants) formed targets, to which the participants were asked to respond [120].

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[119] In which trains of standard tone stimuli were interspersed occasionally with a deviant tone.

[120] In order to keep attention focused on the central fixation point (thereby reducing the chances of the participants inappropriately overtly or covertly switching attention between both visual fields and therefore confounding the supposed 'non-attend' condition monitoring both relevant and irrelevant stimulus sequences), the target to be responded to was always presented in the same visual field. In Hillyard and colleagues' design, the target to be responded to was sometimes in the right and sometimes in the left visual field.

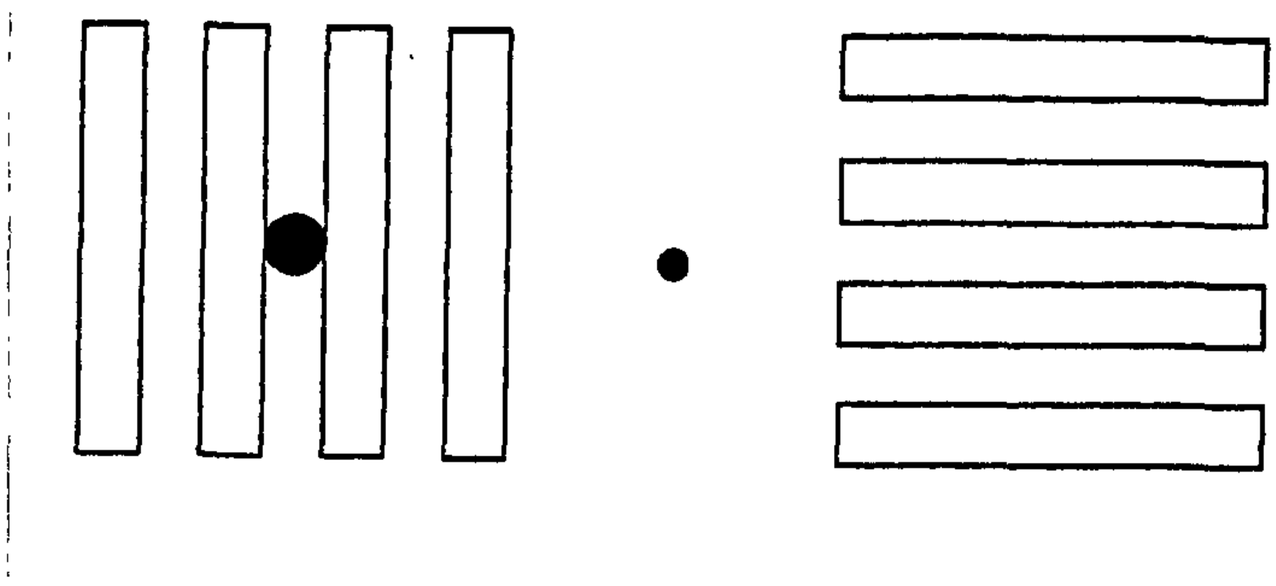
Although auditory MMN can be obtained when participants are attending to the standards and deviants it is seen more clearly in non-attend conditions[121] (Näätänen, 1990). The clearest 'potential' VMMN response should therefore appear over the occipital hemisphere contralateral to the unattended visual field [122]. The occurrence of a VMMN response over this hemisphere would therefore also indicate that it could be elicited in the absence of attention.

METHOD

STIMULI

Figure 3.3 illustrates the stimuli used in pilot study one. The grid pattern of the stimuli represented a complex patterned stimulus (to which the primary visual cortex is more sensitive than to luminance change alone). The stimuli were designed to result in an equal spread of luminance across the visual fields, with the upper and lower and nasal and temporal fields stimulated equally.

Figure 3.3 Stimuli used in Pilot Study 1.



A green dot appeared constantly at the centre of the location of the 'to-be attended' stimuli to help participants attend here.

The standard stimulus consisted of four vertical white bars and the deviant stimulus consisted of four horizontal white bars, presented upon a black background. The deviant and standard stimuli were equal in luminance. The bars were presented 5° the right or left of the central fixation point and each bar measured 8 cm in height and 1cm in width on screen.

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[121] In attend conditions the MMN is overlapped by the N2b-P3a complex, making the MMN difficult to discriminate.

[122] Such a lateralisation would indicate that like the auditory MMN, the VMMN is an early modality-specific effect, because at higher levels in the visual system, information from the right and left visual field are not separate as they are in V1 and the early supplementary visual areas.

As Alho et al., (1992) had suggested that a visual MMN may have a higher threshold for elicitation than the auditory MMN and therefore might need greater degrees of deviance to be elicited, the degree of orientation, i.e., vertical versus horizontal was chosen to ensure that the deviant visual stimuli were very different from the standards.

PARTICIPANTS

Twelve individuals participated, 8 female and 4 male; age range 24 to 43 years (mean 32 years). All participants had normal or corrected to normal vision, were right handed, had no known neurological disorder and were not taking medication. Participants were recruited from the University of Bristol undergraduate and postgraduate student population; none was paid for participation.

PROCEDURE

The stimuli were presented on a computer monitor screen situated one metre in front of and central to, the participants' eye level. The task was to attend to the LEFT visual field while maintaining eye fixation on the central fixation point and to detect and respond, (by pressing a button with the right thumb) to the target (i.e., the deviant stimulus, i.e., the vertical white bars) that was embedded in the stream of standard stimuli presented to the LEFT visual field.

Attention was therefore directed covertly while the participants gaze remained fixated on the central fixation point. Absence of eye movement following stimulus presentation was verified by electro-oculographic methods. The participants were instructed to ignore anything that happened on the right side of the screen and to reduce blinking to a minimum.

The stimuli were presented one at a time, either to the left or right in a randomised fashion. The stimuli appeared with a randomised inter-stimulus interval (ISI) of 612-642 msec, for a duration on screen of 200 msec. The standard and deviant stimuli appeared randomly, but with at least two standards preceding each deviant stimulus. Targets and deviants were presented in random sequence among the standards, each appearing at a mean interval of 11.3 sec. The ratio of standards to deviants to targets was 16:1:1. For each participant 32 trials were recorded; a break was given after 16 trials (each block of 16 trials took approximately 10-15 minutes).

ELECTROPHYSIOLOGICAL RECORDING PARAMETERS

Evoked potentials were recorded from 12 electrodes (F7, FZ, F8, C3, Cz, C4, T3, T4, Pz, O1, Oz, O2) with respect to mastoids in common reference[123]. The signals were amplified (time constant 3 sec; high frequency filter 70 Hz). The 512 msec epochs were digitised at 1000Hz by a 12 bit analogue to digital converter and averaged after rejection of epochs containing high amplitude artefacts. Data was collected until responses to 32 deviants had been averaged.

DATA ANALYSIS

The mean ERP traces for the non-attended standard and deviant stimuli over a 512 msec epoch are displayed in figure 3.4. The data was re-referenced to Fz, to provide a clearer indication of what was happening over the occipital cortex, (which may have been masked by the contribution of 'occipital activity' at the mastoid sites).

The point by point comparison of the standard and deviant stimuli over the 512 msec period of measurement illustrated by the yellow significance bars (a result of a series of 512 individual t-tests comparing the standard and deviant stimuli) for all electrode sites, helped to identify regions of interest over this period of measurement[124]. The method was not used for formal statistical analysis and Bonferroni corrections for multiple comparisons were not applied.

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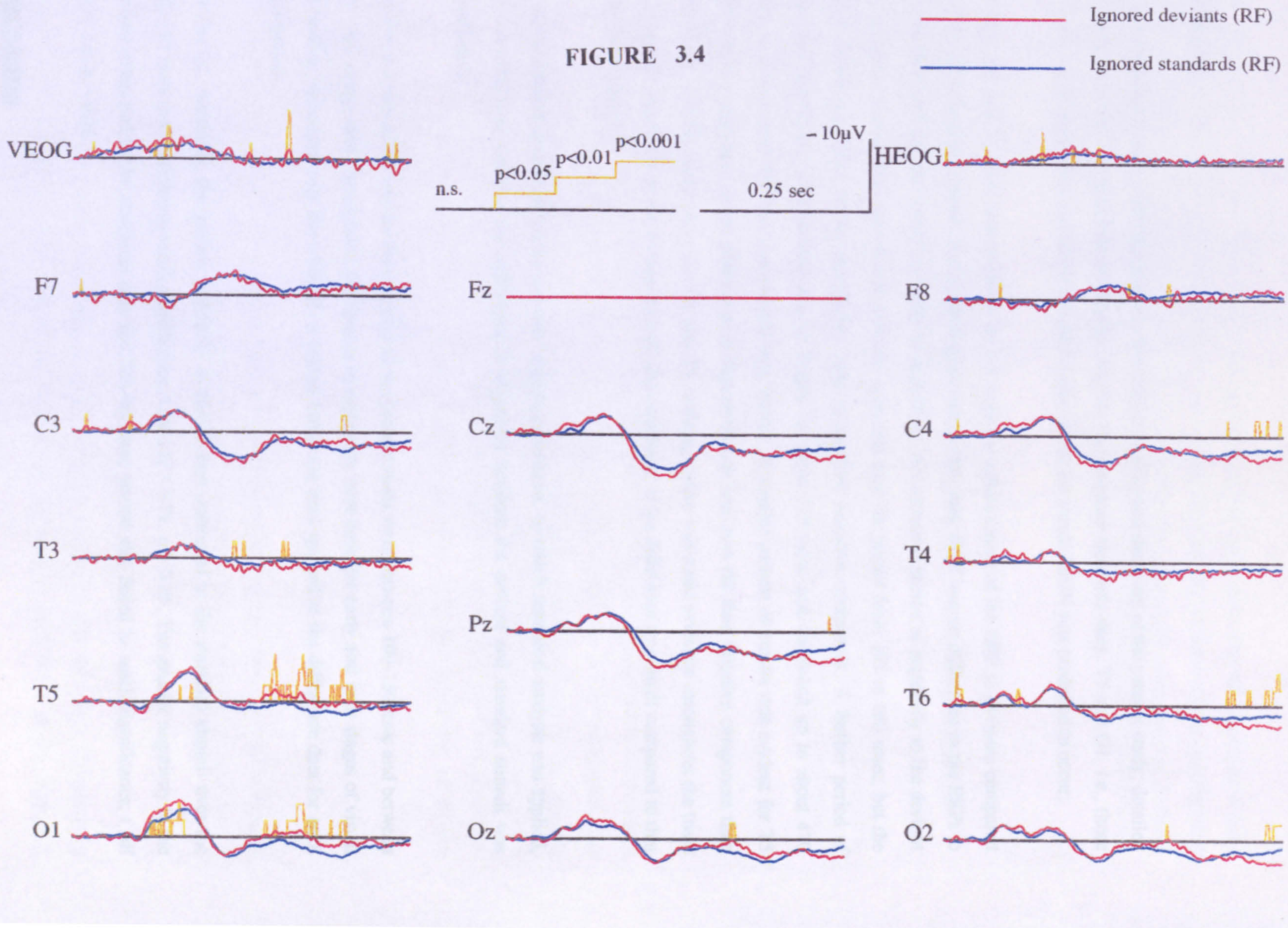
[123] For this experiment and all those that follow : An Archimedes computer and SLE 16 channel EEG machine was used for data acquisition together with a second Archimedes computer and a NEC monitor for stimulus presentation. Skin preparation using abrasive gel was performed and the silver/silver chloride chloride electrodes were positioned according to the international 10/20 system and retained in place using electrode paste and pads.

[124] These yellow bars were also used to indicate regions of interest in the results of subsequent studies.

FIGURE 3.4


Ignored deviants (RF)
Ignored standards (RF)
VEOG
HEOG
n.s.
p<0.05
p<0.01
p<0.001
– 10μV
0.25 sec
F7
Fz
F8
C3
Cz
C4
T3
T4
Pz
T5
T6
O1
Oz
O2

RESULTS

A detailed description of the effects at all electrode sites is beyond the remit of the present study; detailed statistical analysis was therefore performed only for the posterior electrode sites, T5 and O1, i.e., those over the left occipital and occipito-temporal region; where the visual MMN was predicted to occur.

At both O1 and T5 there was evidence for the negative enhancement of the ERP to deviants compared to that of the standard stimuli. At O1, during the initial 100 msec there was no difference in the ERPs to the standard and deviant stimuli in terms of negativity. An increased period of negativity to the deviant compared to the standard stimuli was however apparent over the period from 109 to 180 msec, but the traces converged again on the descending limb of the first negative component. A further period of increased negativity to the deviant stimuli began at about 219 msec and continued up to about 470 msec, at which time the traces converged once again. A similar pattern of results was evident for T5 although the amplitude of the difference in negativity was less over the first negative component than seen at O1. (At electrode sites Oz, O2 and T6, although there was some evidence throughout the trace for a greater negativity to the deviant stimuli, the amplitude of the difference was small compared to that seen for O1 and T5).

It was decided to divide the traces into two 'regions of interest' to which statistical analysis was applied, (i.e., to determine whether this difference in negativity between the deviant and standard stimuli was significant).

The two periods of interest for the purposes of the present study were between 100-150msec and between 280- 400 msec; thus representing differences in negativity over both the early and later stages of visual processing associated with the VMMN. A paired t test was then applied to the difference data for each time period.

For the O1 electrode, the greater negativity to the deviant compared to the standard stimuli over the 100-150 msec period failed to reach significance, t (df 11) = 0.74, $p > 0.05$. The greater negativity to the deviant compared to the standards over the 280-400msec period also failed to reach significance, t (df 11) = 1.8, $p > 0.05$.

DISCUSSION

Although not statistically significant, the results of pilot study one provided evidence that a more negative ERP could be elicited in response to deviant compared to standard visual stimuli and furthermore that this difference occurred in the absence of attention. That the greater negativity to the deviants was seen in the occipital and occipito-temporal area (i.e., indicated by the ERPs at O1 and T5)

and the fact that a greater Visual mismatch negativity is observed over the left hemisphere (i.e., contralateral to the right visual field where they were presented) illustrated the modality-specificity of this effect. The characteristics of the results of this study therefore resembled those found in auditory MMN and implied that a visual analogue of the auditory MMN might exist though the stimuli used has not produced a strong effect.

3.27 (b) PILOT STUDY TWO: A REPEAT OF STUDY ONE, BUT WITH PARTICIPANTS ATTENDING TO THE RIGHT VISUAL FIELD.

To ensure that the trends observed in Study One were not simply a result of hemispheric differences in processing, Study One was repeated but with the non-attended standard and deviant stimuli presented to the opposite hemisphere.

PARTICIPANTS

A different group of individuals was used to perform study two. This prevented possible confounding effects of the participants' prior knowledge of the study. Using a different set of participants also removed the possible confusion of them being asked to attend and respond to stimuli to the opposite visual field to which they had previously attended [125]. Twelve individuals participated, 8 female and 4 male, age range 20 to 43, mean 28 years. All had no neurological disorders, were not taking drugs and had normal or corrected to normal vision. All were recruited from the University of Bristol undergraduate and postgraduate population.

PROCEDURE

The procedure and electrophysiological measurement parameters for study two were identical to those of study one except that individuals were asked to detect and respond to targets in the RIGHT visual field.

RESULTS

The treatment of the results was identical to that used for study one and the mean difference in negativity between the standard and deviant stimuli are presented in table A3.2 of the chapter 3 appendix.

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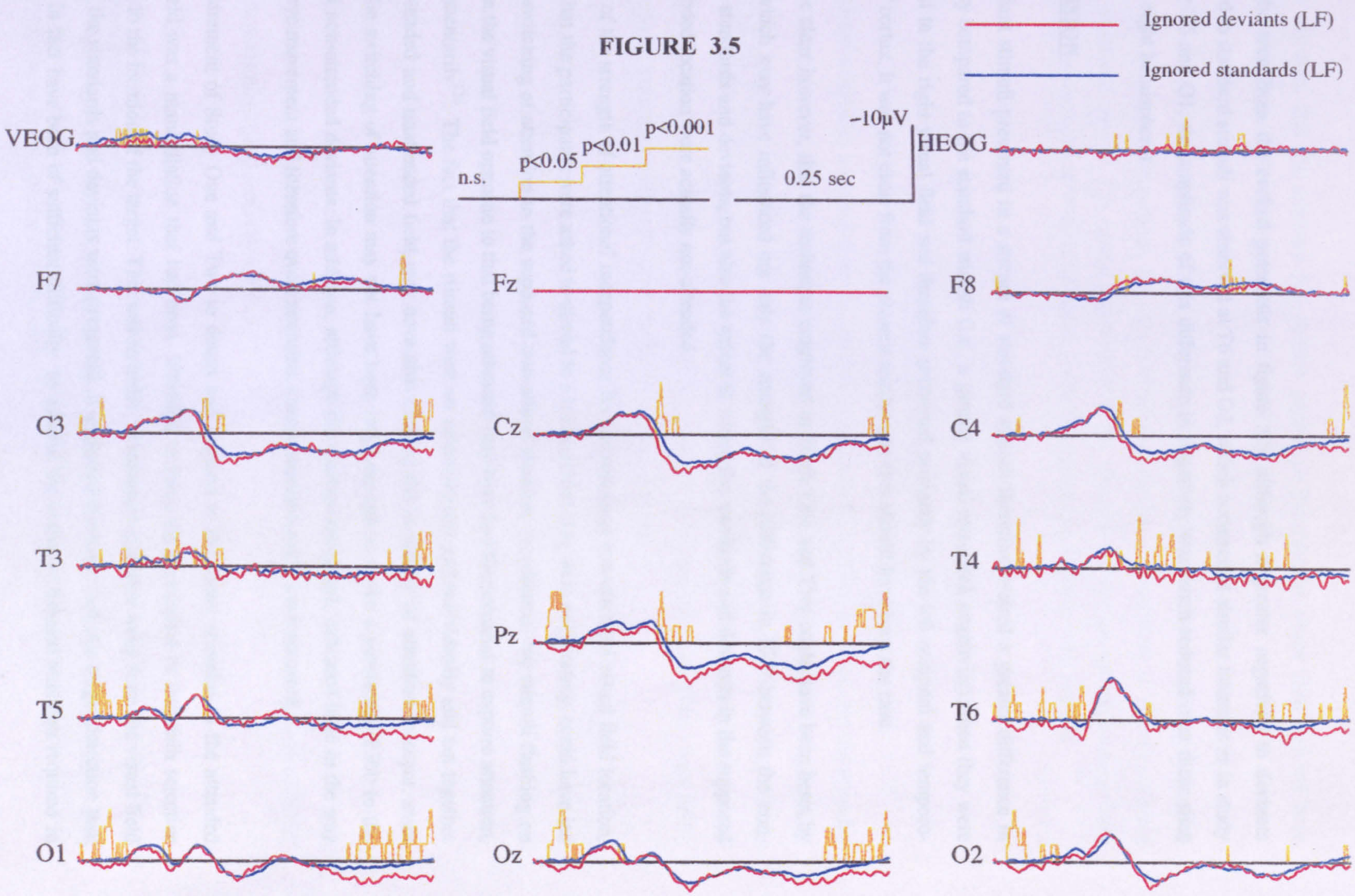
[125] There was no significant difference between the age of the two groups of participants in study one and two, therefore indicating that any differences in results would not be due to confounding factors of age differences.

Because the standards and deviants were presented to the right visual field, the VMMN would be expected to be prominent at T6 and O2, the right occipital and occipitotemporal regions of the right hemisphere. Figure 3.5 illustrates the ERPs elicited to the non-attended standard and deviant stimuli which were presented to the Left visual field.

FIGURE 3.5


Ignored deviants (LF)
Ignored standards (LF)
VEOG
HEOG
n.s.
p<0.05
p<0.01
p<0.001
−10μV
0.25 sec
F7
Fz
F8
C3
Cz
C4
T3
T4
Pz
T5
T6
O1
Oz
O2

As can be seen from the evoked potentials in figure 3.5, although a greater negativity to deviants compared to standard stimuli was observed at T6 and O2, which occurred at similar latencies as in study one over T5 and O1, the amplitude of this difference in negativity was much reduced over these sites (i.e., the right hemisphere).

DISCUSSION

The deviant stimuli presented in a stream of standard stimuli therefore evoked a greater difference in negativity compared to the standard stimuli (i.e., a greater visual mismatch negativity) when they were presented to the right visual field and therefore processed primarily by the left occipital and temporo-occipital cortex. It was not clear from the present results why this should have been the case.

It became clear however, that the technique employed in Study One and Two could have been beset by factors which may have influenced not only the strength of the difference in ERP between the non-attended standards and deviants, but also the extent to which the standards and deviants in the supposed non-attended location were actually not-attended.

In terms of the strength of attentional independence for the supposed non-attended visual field location, the fact that the participants were asked to attend to a location that they were not fixating, could have led to some switching of attention to the supposed non-attend location. In addition, the stimuli flashing on and off in the visual field opposite to that being attended may have had the potential to capture attention, even momentarily[126]. The fact that the stimuli were on intermittently and individually and not together in the attended and unattended field may have also enabled the switching of attention to occur, even though the switching of attention may not have been large enough to evoke a substantial P300 to the supposed non-attended deviants. In addition, although the electro-oculograph indicated little in the way of overt eye movement and therefore overt attention, covert attention could have occurred.

The requirement of Study One and Two to detect and respond to the target stimulus in the attended visual field was a manipulation that had been intended to force the participant to maintain selective attention to the location of the target. This was in order to maintain attention away from the visual field in which the standards and deviants were presented. It appeared however, that this target detection task may not in fact have been of sufficient difficulty to achieve the extent of focused attention required in

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[126] Although visuospatial attention and gaze are typically oriented towards the same location (e.g. Abrama and Dobkin, (1994), visuospatial attention can be oriented covertly in the absence of overt eye movements (e.g. Posner 1980). In fact numerous studies have shown that when individuals are asked to keep gaze constant, relatively automatic and covert shifts of visuospatial attention are induced by a luminance increment (i.e., an exogenous cue) in the periphery (e.g., Jonides and Yantis 1988).

order to maintain that the standard and deviant stimuli in the opposite visual field had not been attended[127] (Näätänen, 1997, personal communication).

A further study, study three, was therefore designed to not only elicit a VMMN under more stringent conditions of attention independence, but also to determine whether the amplitude of VMMN reflected the type of stimuli used[128]. The central presentation of the standard and deviant stimuli in study three also enabled the similarity of VMMN production in both occipital hemispheres to be assessed.

3.28 STUDY 3.

In an attempt to achieve a greater focus of attention away from the location at which the non-attended standard and deviant stimuli were presented, the participants in this study were required to both fixate and attend to a central location[129], where a target, which had to be responded to by a button press, was presented. It was hoped that participants would find it subjectively easier to maintain attention to the fixation point and not 'feel that their eyes were being captured to the opposite side of the visual field', thus helping to maintain selective attention to the appropriate location.

Instead of using horizontal and vertical bars, study three used a single vertical bar and a double vertical bar as standards and deviants respectively, in order to determine whether a different type of stimulus change would elicit a greater negative enhancement than that elicited in studies one and two.

The design of the stimuli in study three also took into account the applicability of the technique to the potential measurement of visual MMN in older individuals and those with Alzheimer's disease. Attending to a central position would be easier to manage particularly for individuals with AD[130], who may find the instructions to fixate on the centre spot but to attend to either the left or right visual field, difficult to understand and to comply with.

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[127] A major requirement for any visual mismatch negativity was that it could be elicited automatically, i.e., independently of attention.

[128] Using horizontal versus vertical deviants may have been a change in stimuli that did not have much significance within the visual system (see Alho et als' 1992 suggestion that a visual MMN might be sensitive to changes in only certain stimulus features).

[129] The focus of visual attention normally coincides with the direction of gaze and since deviance-related negativity has not been reported (in the published literature) when attention is diverted from the stimulus change by fixation elsewhere in the visual field it was thought that this would provide a better test of the automaticity of any elicited visual mismatch negativity.

[130] There are reports that in AD there may be abnormalities in eye movements and fixation stability, (Hutton, Nagel, Loewenson, 1984; Fletcher and Sharpe, 1986, 1988). Schlotterer et al (1984) also found that individuals with AD require longer exposure times in order to identify visual stimuli (see also Hart and Semple 1990).

3.28(a) STIMULI

Figure 3.6 illustrates the stimuli used for study three.

The standard stimulus consisted of a single white bar; the deviant stimulus was a double white bar (of equal luminance and overall area to the single white bar). Both standards and deviants were simultaneously presented symmetrically above and below the central fixation square in the unattended space.

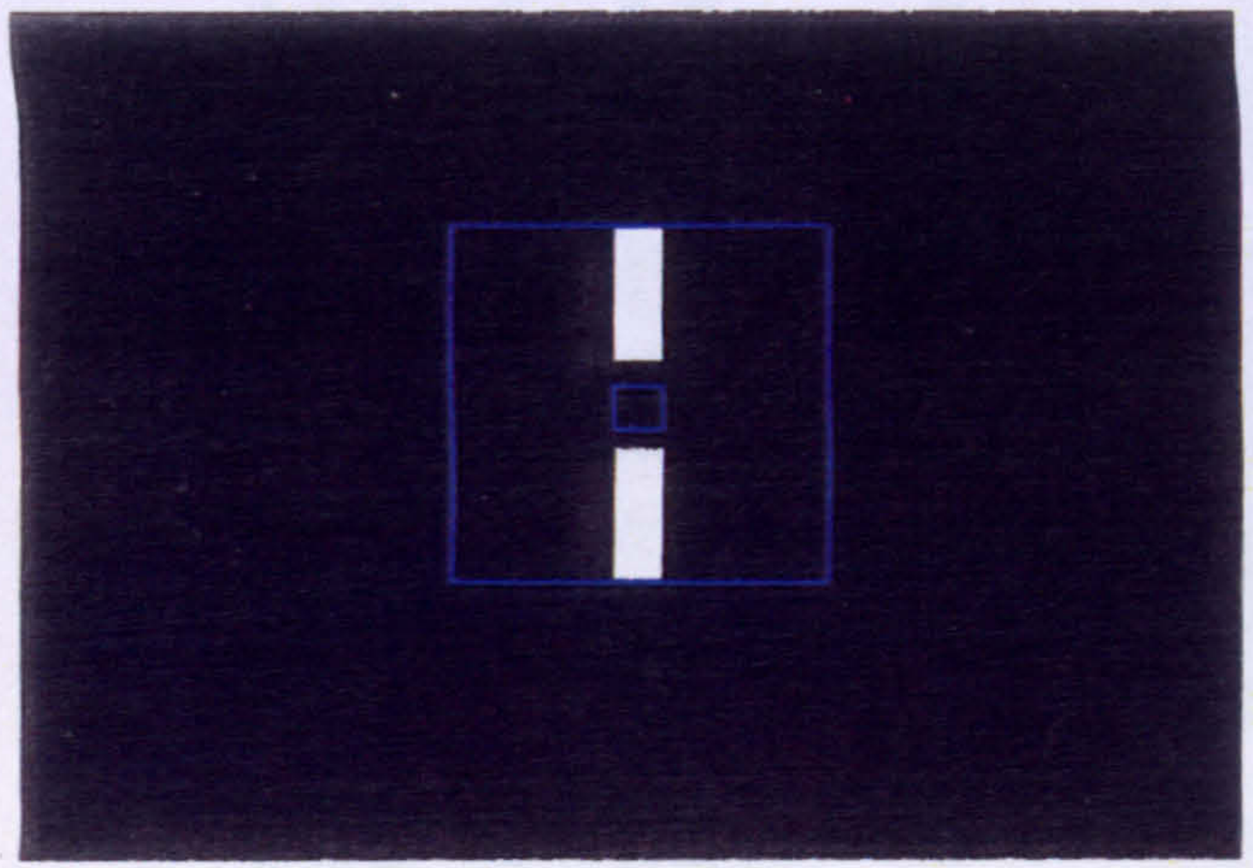
The outer blue frame was 10.5 x 10.5 cm and the inner, central blue frame was 1.2 x 1.2 cm on screen. The standard, single white bars were 4.6 x 1.2 cm; deviants were double white bars; 4.6 x 0.6 cm on screen; 0.6 cm apart.

3.28(b) PARTICIPANTS

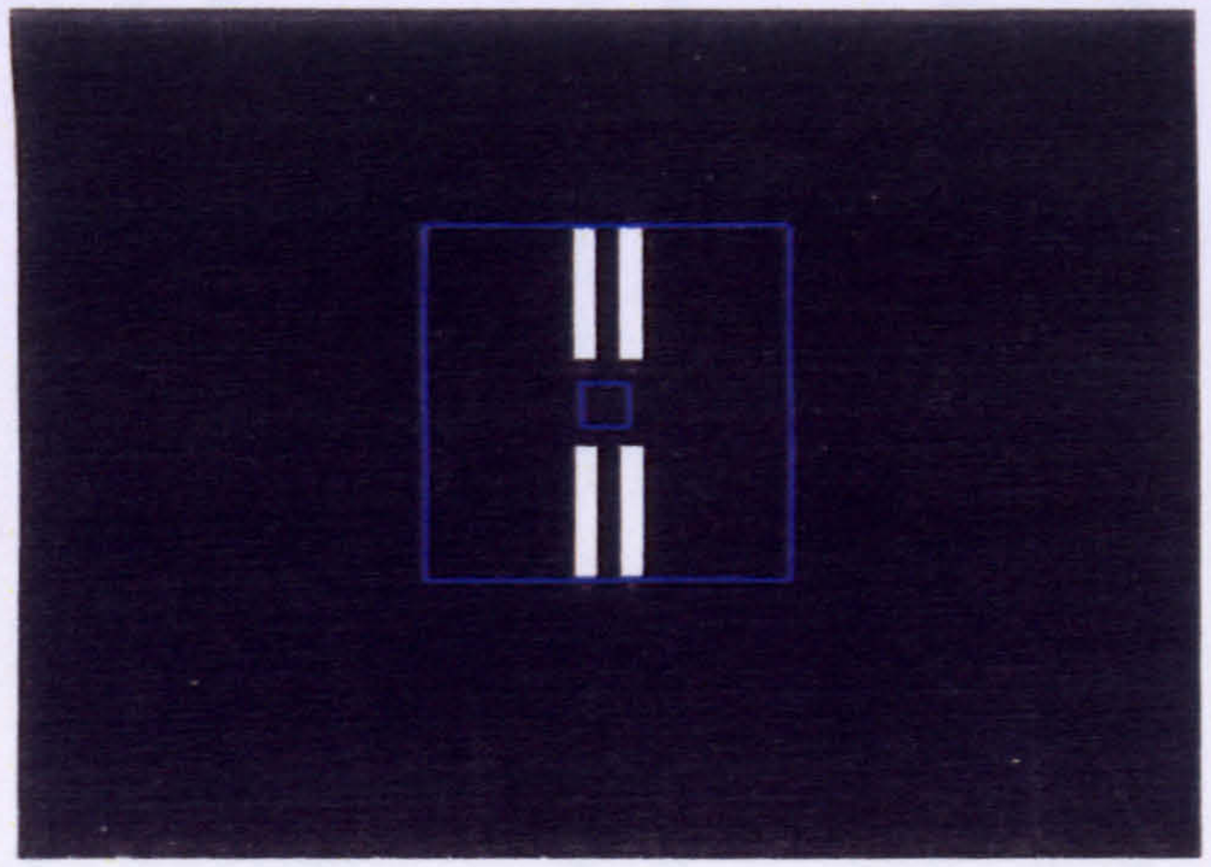
Twelve participants took part, 8 female;4 male, age range, 24 to 43, mean age 32 years. All participants had normal or corrected to normal vision, had no neurological disorders and were not on medication. Participants were recruited from the general public and the University of Bristol postgraduate and undergraduate student population. None of the participants was paid for taking part.

FIGURE 3.6

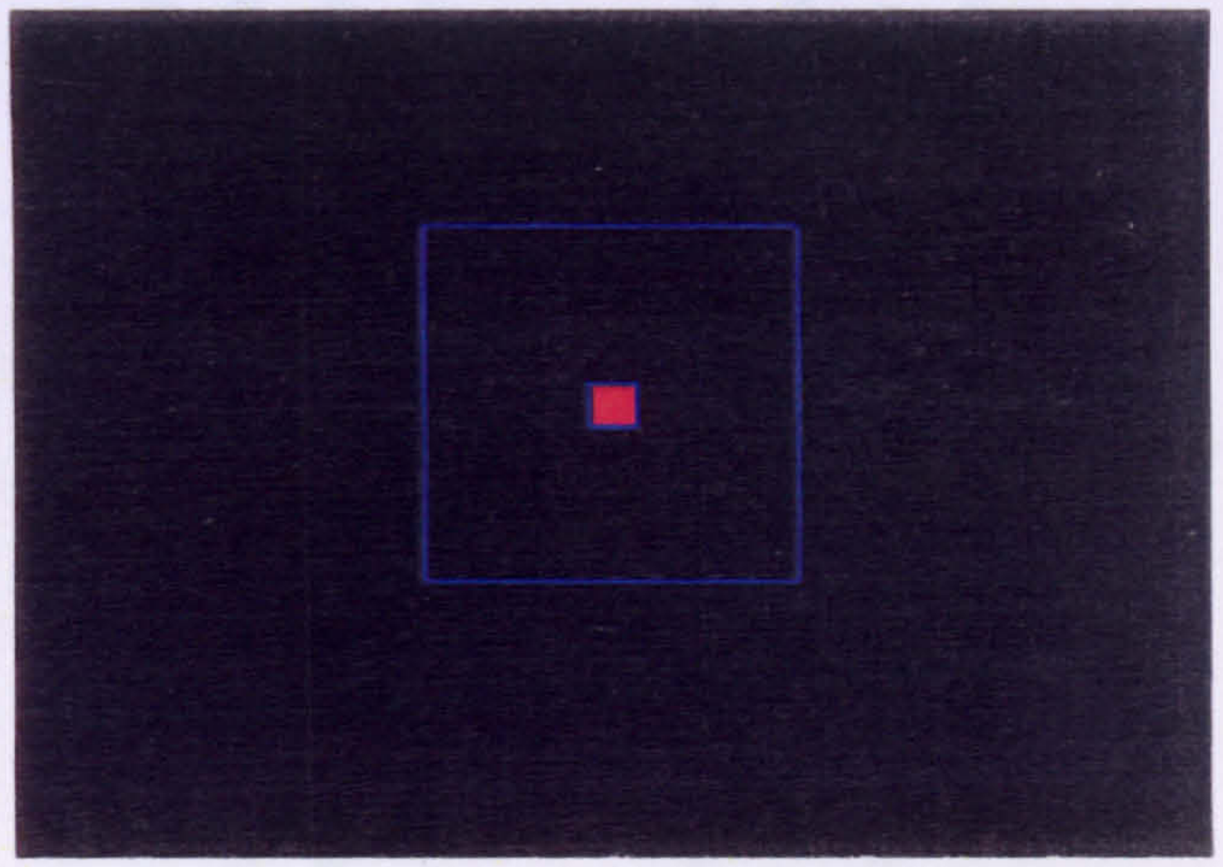
Stimuli used to elicit the ERPs



Ignored Standard



Ignored Deviant



Attended Target

3.28(c) PROCEDURE

Participants were seated one metre away from the centre of the computer screen and instructed to fixate and attend to the area bounded by the small central blue square and to ignore everything outside of that region for the duration of the trial. Participants were also instructed to detect and respond to the target, a red square which filled the area bounded by the small central blue square, by pressing a hand held button.

Periodically the white bars appeared with a randomised ISI of 612-642 msec, for a duration on screen of 200 msec. Targets and deviants were presented in random sequence among the standards, each appearing at a mean interval of 11.3 sec, with at least two standards preceding a deviant stimulus. The stimulus repetition rate was maximised (within the limits of the evoked potential epoch time and digital acquisition process).

The ratio of standards to deviants to targets was 16:1:1. The target did not appear at the same time as the deviant or standard stimuli and 32 responses to deviants were recorded for each participant. It was predicted that the central rather than lateralised stimulus presentation would evoke VMMN over both occipital hemispheres.

The target presentation was designed to be a rare event meaning that the participants had to attend well and concentrate hard on the fixation area not to miss the target[131], which they had to detect and respond to[132].

The symmetrical location of standards and deviants about the target area was intended to minimise any tendency for attention or fixation to be biased away from the attended target area. This method of presentation also ensured that there was equal luminance above and below the fixation point; thereby reducing any differences in processing between the cortex involved in the processing of the upper and lower visual fields which may result in different ERP patterns, particularly at the occipital electrodes[133] (Gunter, Wijers, Jackson and Mulder, 1994).

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[131] Thus developing a sharp attentional focus, thereby reducing the likelihood of attention wandering to the supposed 'non-attend' locations.

[132] Also in this study the target (a red square) was very different from the task-irrelevant standard and deviant stimuli. It was hoped that such a large difference depicting the target from the standards and deviants would prevent participants inadvertently attending to the standards and deviants because they were easily confusable with the target. It was hoped that such measures would ensure that any visual MMN ERP component was not confounded by attention or motor-related components.

[133] ERPs for stimuli presented above fixation are more positive than those presented below it, in the early latency range (100-270 msec). Gunter et al (1994) also found that attending above fixation leads to a more efficient target detection (i.e., a faster RT with similar accuracy) as compared with attending below

High stimulus presentation rates together with short ISIs and random presentation (so no anticipatory actions occurred) and the necessity of focusing on the central fixation to ensure that a target was not missed (as they were presented so rarely and remained on screen for such a short time) provided a high load target selection task which ensured that attention was kept focused thus producing optimum conditions for VMMN production (Woldorff et al. 1990).

3.28(d) ELECTROPHYSIOLOGICAL RECORDING PARAMETERS

Evoked potentials were recorded from 12 electrodes (F7, FZ, F8, C3, Cz, C4, T3, T4, Pz, O1, Oz, O2) with respect to mastoids in common reference (subsequently re-referenced to Fz). The signals were amplified (time constant 3 sec; high frequency filter 70 Hz). The 512 msec epochs were digitised at 1000Hz by a 12 bit analogue to digital converter and averaged after rejection of epochs containing high amplitude artefacts. Data was collected until responses to 32 deviants had been averaged.

The resultant ERP waveforms are displayed in figures 3.7, 3.8 and 3.9.

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fixation. Statistically significant differences between potential fields elicited by upper and lower retinal stimulation has also been found, for a review see Skrandies, 1995).

FIGURE 3.7 (12 Young Adults).

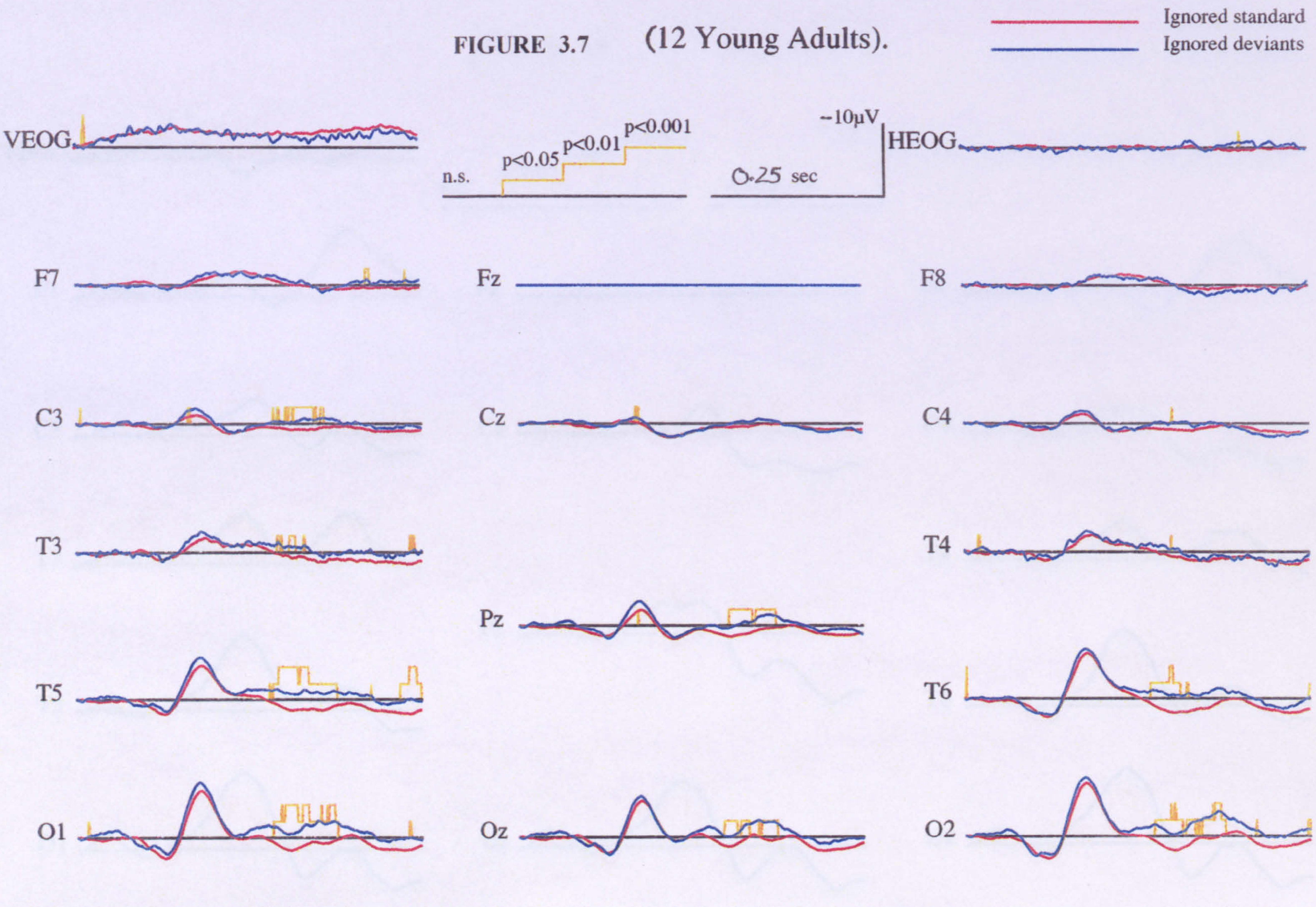


FIGURE 3.8 (12 Young Adults).

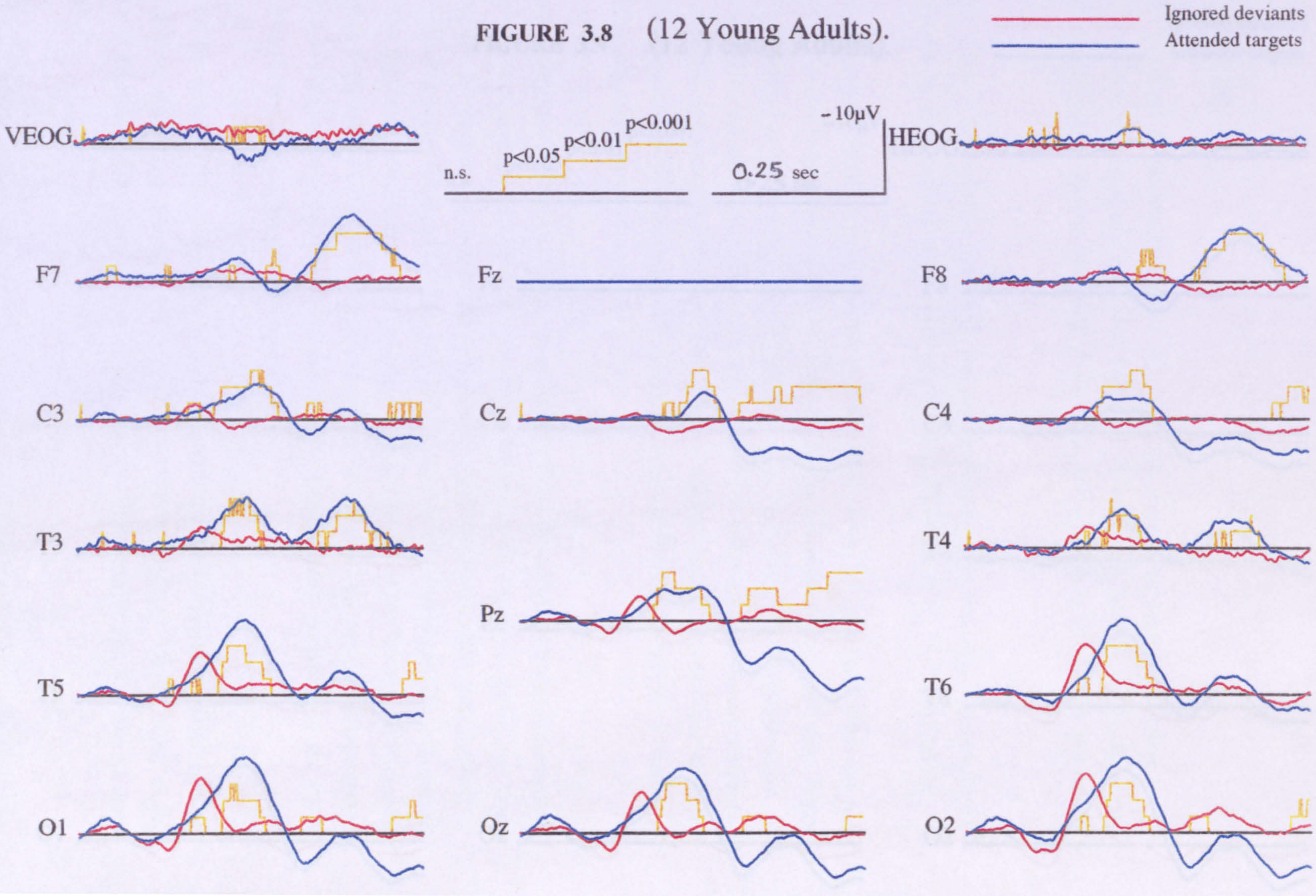
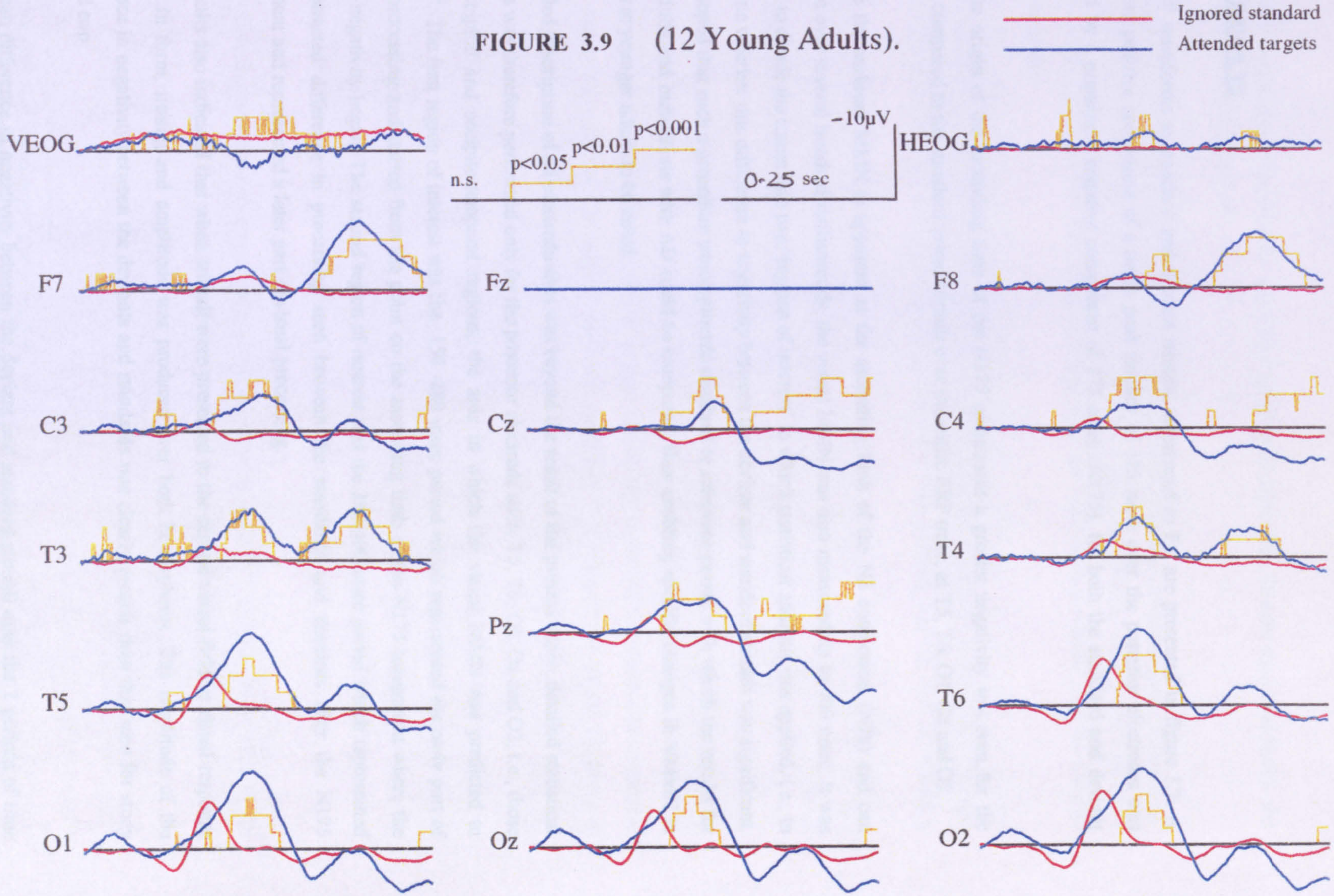


FIGURE 3.9 (12 Young Adults).



3.28(e) RESULTS

The ERP waveforms to standard and deviant stimuli, referenced to Fz, are presented in figure 3.7. A prominent positive component of a mean peak latency of 125 msec over the posterior electrodes was followed by a prominent negative component of 175 msec (N175), for both the standard and deviant stimuli.

From the origin of the ascending limb of the N175 component a greater negativity was seen for the deviant compared to the standard visual stimuli over the entire ERP trace, at T5, T6, O1, Oz and O2.

Because the auditory MMN is apparent at the ascending limb of the N2 component (N2a) and can continue over several hundred milliseconds, the visual MMN was also measured up to 400 msec. It was decided to divide the traces into two 'regions of interest' to which statistical analysis was applied, i.e., to determine whether this difference in negativity between the deviant and standard stimuli was significant. It was hoped that such a procedure would provide standard or reference points with which the results for older adults and individuals with AD could be compared, thus enabling specific changes in VMMN in relation to younger adults to be noted.

A detailed description of all electrode sites was beyond the remit of the present study; detailed statistical analysis was therefore performed only for the posterior electrode sites, T5, T6, O1, Oz and O2, i.e., those over occipital and occipito-temporal regions, the area in which the visual MMN was predicted to occur[134]. The first region of interest was the 150 -280 msec period which represented the early part of visual processing and started from the point on the ascending limb of the N175 component where the greater negativity began. The second region of interest was the 280-400 msec period which represented the protracted difference in processing seen between the standards and deviants after the N175 component and represented a later part of visual processing.

The results also indicated that when stimuli were presented to the central visual field a visual response similar in form, timing and amplitude was produced over both hemispheres. The amplitude of the difference in negativity between the deviants and standards was clearly greater than that seen for study one and two.

The mean difference in negativity between the deviant and standard stimuli over the 2 periods of time (150-280 and 280 - 400 msec) at electrode sites T5, T6, O1, O2 and Oz, are presented in table A3.3 of

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[134] The point by point comparison of the standard and deviant stimuli over the 512 msec period of measurement illustrated by the yellow significance bars (a result of a series of 512 individual t-tests comparing the standard and deviant stimuli) for all electrode sites, served to illustrate regions of interest over this period of measurement.

the chapter 3 appendix. A paired t-test was then applied to the difference data for each time period and resulted in the following findings:

The greater negativity to the deviant than to the standard stimuli, over the 150-280 msec time period did reach significance at T5, t (df 11) = 4.75, $p < 0.001$; T6 , t (df 11) = 3.31, $p < 0.01$; O1 t (df 11) = 5.63, $p < 0.001$; O2, t (df 11) = 4.58, $p < 0.001$; and Oz, t (df 11) = 4.48, $p < 0.001$ over the 150-280 msec time period.

The same was true for the 280 to 400 msec time period; T5, t (df 11) = 5.27, $p < 0.001$; T6, t (df 11) = 3.61, $p < 0.01$; O1 t (df 11) = 6.00, $p < 0.001$; O2, t (df 11) = 4.65, $p<0.001$; and Oz, t (df 11) = 4.58, $p < 0.001$.

3.28(f) DISCUSSION OF RESULTS

The significantly greater negativity to the deviants than to the standards at T5, T6, O1, Oz and O2 over the 150-280 msec time period (i.e., that surrounding the visual N175 component), indicated an enhanced negativity to the unattended deviant stimuli that closely resembled that elicited by unattended deviant auditory stimuli; i.e., the auditory mismatch negativity. The protracted increased negativity to the deviant stimuli resembled the waveform seen in auditory mismatch negativity.

The latency of the N175 was the same at both O1 and O2. There was a slightly greater amplitude of both deviants and standards in the right occipital cortex, but with very little difference in the amplitude of the difference in negativity between O1 and O2 over both periods of interest[135]. The amplitude was smallest at Oz. Similar amplitude of difference between standards and deviants for the later aspects of the response were also similar for the right and left occipital cortex[136].

The negative augmentation to deviant visual stimuli occurred only over the posterior cortex, in the region of the occipital and occipitotemporal visual cortex, indicating a modality-specific visual mismatch negativity[137].

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[135] See table A3.3 of the chapter three appendix.

[136] A hemispheric difference between the amplitude of mismatch negativity had been found in the auditory modality. In audition, the greater MMN amplitude had occurred over the right compared to the left hemisphere irrespective of the ear of stimulation (Lavikainen, 1997).

[137] There was some indication that the greatest significant difference values between the standard and deviant stimuli occur in the left visual cortex (i.e., T5 and O1 for both 150 - 280 and 280-400 msec periods) so there may be some asymmetry involved. These differences need to be determined statistically in future research. In auditory MMN larger amplitudes of MMN have been found over the right compared to the left hemisphere (Laavikainen, 1997).

Figures 3.8 and 3.9 which illustrate the ERP elicited to the deviant and standard compared (respectively) to that of the target stimuli, indicate that whereas a substantial P300 is elicited to the target stimuli this was not the case for either the standards or deviants. This result is best seen at Pz and in view of the fact that the P3b component is generally considered (e.g. Picton, 1992) to be elicited only by attended stimuli (particularly targets), its absence particularly at the supposed unattended deviants and standards confirmed that attention had indeed been focused away from the 'non-attend' location.

This finding therefore demonstrated the important effect that the VMMN could be evoked automatically, i.e., independently of attention and appeared to reflect automatic change detection in the visual environment.

That a greater amplitude of VMMN was produced in the present study compared to study one and two may have indicated that the stimuli used in study three i.e., single and double lines were better at evoking VMMN than a change in orientation of the bars i.e., from vertical to horizontal.

Evidence provided by Study Three for the existence of a visual analogue of the auditory mismatch negativity include:

1) **The enhanced negativity to the unattended deviant compared to the standard stimuli commencing around the 'N2' (N175) component and continuing for several hundred milliseconds.**
2) **The occurrence of the negativity over the posterior occipital and temporo-occipital electrodes indicating its visual modality- specificity and a possible locus of its generator processes within the primary, striate or secondary, extrastriate visual areas.**
3) **That it is independent of attention.**

The enhanced negativity of the visual ERP to the deviant compared to the standard stimuli can be explained in a similar manner to which Näätänen explained this phenomenon in the auditory modality.

The similarity between the standard and deviant stimuli ERPs in the early stages of processing, i.e., 0-150 msec at posterior electrode sites indicated that because the standards and deviants were matched in terms of luminance and overall area, their resultant sensory or early visual processing was comparable. The subsequent neural representation of their shape however[138], could have resulted in the production of two different traces; which when compared by a mis-match detector' resulted in a signal being sent to subsequent, higher-level processes, 'warning them' that a potentially important change had occurred in

[138] The VMMN may (as suggested for the auditory MMN) therefore reflect the results of the automatic comparison of incoming stimuli to a neural trace representing the physical features of repetitive aspects of the environment.

the visual environment. The result of which may have been the greater allotment of further, higher-level processing resources to the deviant compared to the standard stimuli, culminating therefore in a more negative ERP to the deviant compared to the standard stimuli at later processing stages, (i.e., around the 150-280 and the 280-400 msec range).

3.29 STUDY 4

A repeat of Study 3 and an additional test to determine that the visual mismatch negativity found in study 3 was due to a change in stimuli and not a differential response to the stimuli themselves.

It was important to ensure that the negative augmentation of the ERP to the deviant compared to the standard stimulus found in study three was due to a change or deviance in visual stimuli and not the result of using a particular type of stimulus[139]. The study was repeated therefore with the original stimulus conditions and with the standard and deviant stimuli swapped over. If the negative augmentation to the deviants occurred as a result of a change in a sequence of standard stimuli and not just as a result of the stimuli themselves then an enhanced negativity, i.e., a VMMN should also be seen in response to the single bar when it formed the deviant stimulus.

All the participants were tested with the double bars as the deviant stimuli first (as in the original study, i.e. study 3); followed after a 10 minute interval by the reversed stimuli condition. This was to ensure that the conditions for the second group of people tested for the elicitation of a VMMN were the same as for the original study 3 (i.e., that the task was completely novel to them with the consequence of being be less aware of the presentation of the standard and deviant stimuli outside the focus of attention).

[139] Although the standards and deviants were equiluminant they differed in form, i.e., the number of contours.

3.29(a) METHOD

PARTICIPANTS

Twelve individuals took part (8 female; 4 male) ranging in age from 25 to 42, with a mean age of 31 years. All Participants, recruited from the undergraduate and postgraduate student population of the University of Bristol, had normal or corrected to normal vision and had no neurological disorders and were medication-free. No payment was given for participation.

PROCEDURE

The procedure and electrophysiological recording parameters were identical to that in study 3.

3.29(b) RESULTS AND COMMENTS

Visual mismatch negativity in 24 older adults.

Figure 3.10 illustrates the ERP to the standard and deviant stimuli for a total of 24 younger adults (the 12 from the original study added to the 12 from study 4).

The enhanced negativity of the ERP to the deviant compared to the standard stimuli seen in study three was apparent at the same electrode sites, i.e., T5, T6, O1, Oz and O2 in the present study. The amplitude of this difference in negativity was greater in the present study with 24 participants than in study three with only 12 participants.

For the posterior electrode sites, the mean difference in negativity between the deviant and standard stimuli over 2 different periods of time, 150-280msec and 280 to 400 msec, was measured; the results are displayed in table A3.4 of the chapter 3 appendix. A paired t-test was then applied to the difference data for each time period and resulted in the following findings:

The enhanced negativity of the ERP to deviant stimuli over the 150-280 msec period reached significance at T5, $t\ (df\ 23) = 5.9$, $p < 0.001$; T6, $t\ (df\ 23) = 5.4$, $p < 0.001$; O1, $t\ (df\ 23) = 5.84$, $p < 0.001$; O2, $t\ (df\ 23) = 6.12$, $p < 0.001$; Oz $t\ (df\ 23) = 5.29$, $p < 0.001$.

The same was true over the 280-400msec time period; the ERP to the deviant stimuli were significantly more negative to the deviant than to the standard stimuli; T5 $t\ (df\ 23) = 6.0$, $p < 0.001$; T6, $t\ (df\ 23) = 5.62$, $p < 0.001$; O1, $t\ (df\ 23) = 6.45$, $p < 0.001$; O2, $t\ (df\ 23) = 5.85$, $p < 0.001$; Oz, $t\ (df\ 23) = 5.44$, $p < 0.001$.

FIGURE 3.10 (24 Young Adults).

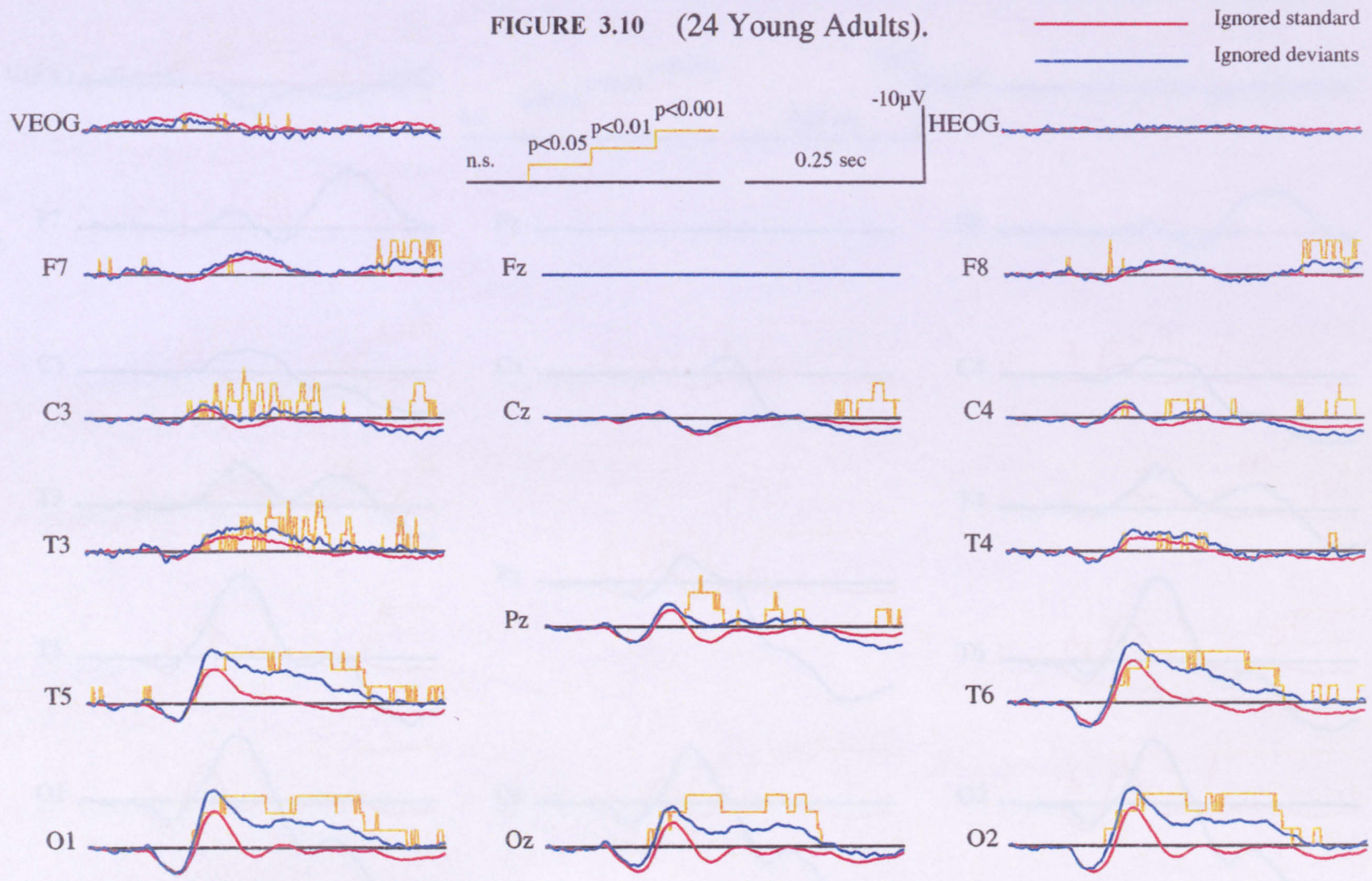


FIGURE 3.11 (24 Young Adults).

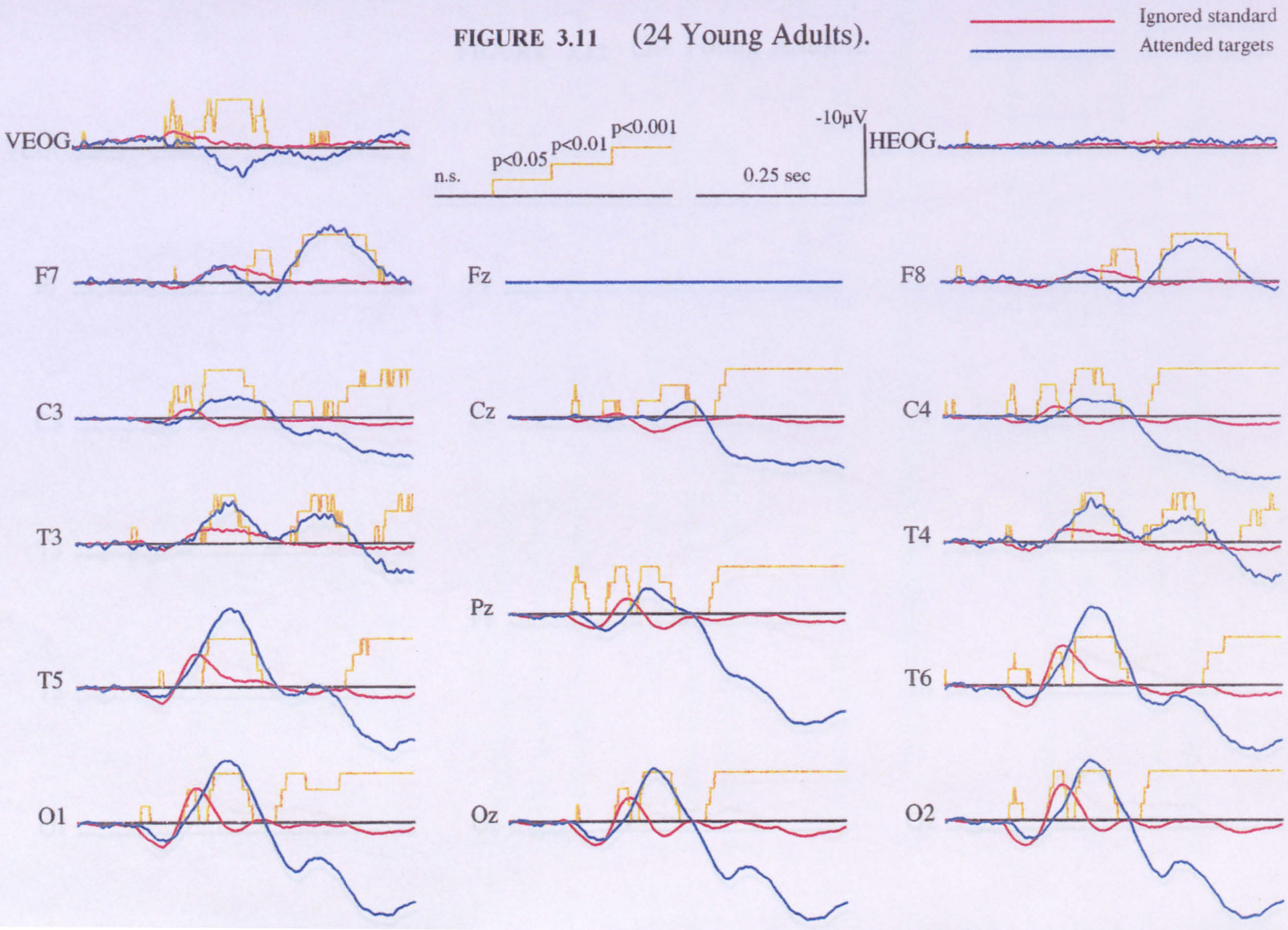
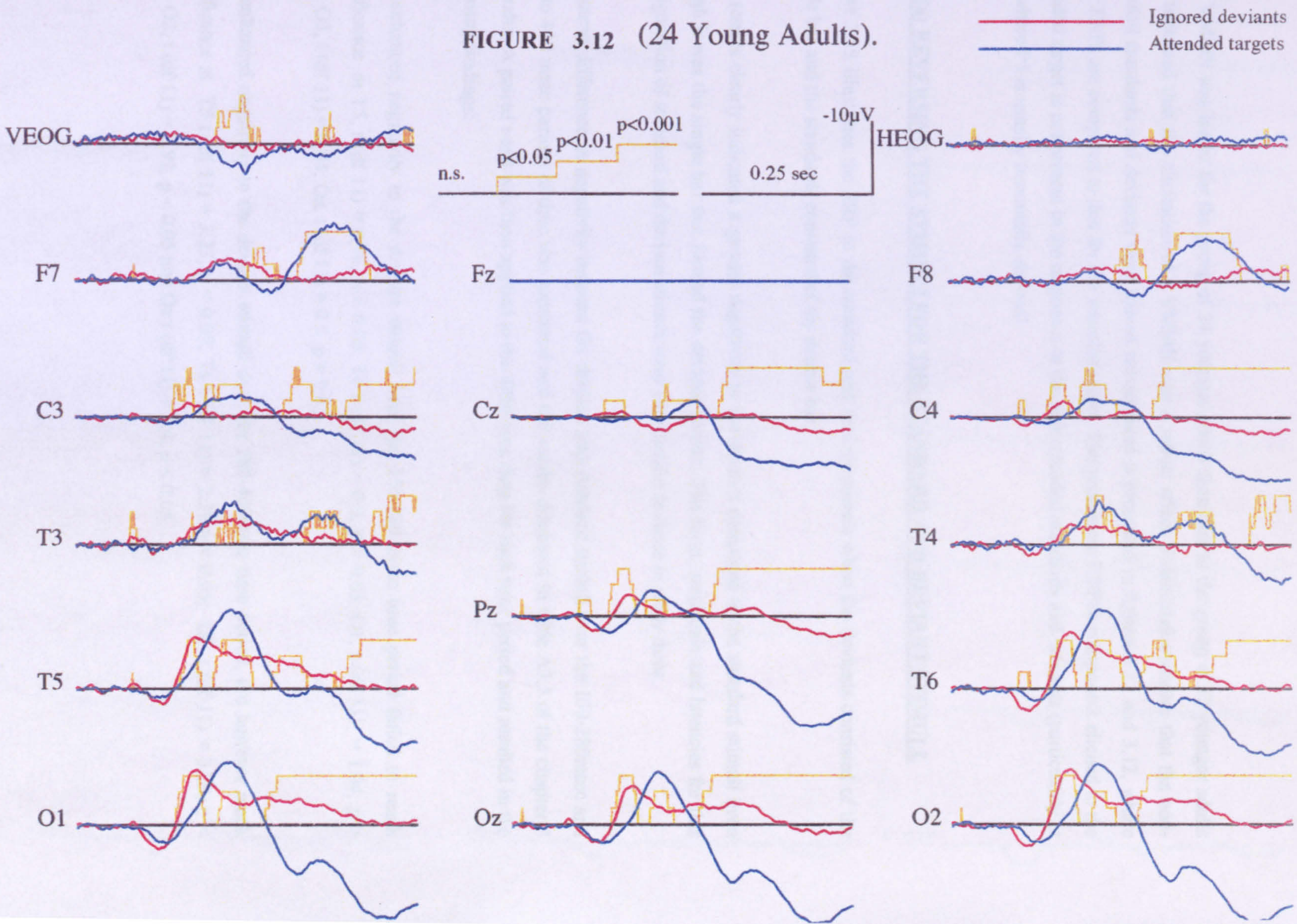


FIGURE 3.12 (24 Young Adults).



The VMMN was larger for the group of 24 younger adults than that to the group of 12 younger adults and indicated that the elicitation of a VMMN was a robust effect. Additional evidence that the non-attended standards and deviants were indeed not-attended is presented in figures 3.11 and 3.12, where their ERPs are compared to that for the attended target. The prominent P3/P3b component elicited to the attended target is not present in the responses to the non-attended standards and deviants (particularly at Pz, where P3 is usually maximally elicited).

3.30(a) REVERSING THE STIMULI FOR THE STANDARD AND DEVIANT STIMULI.

Figure 3.13 illustrates the ERP to the standard and deviant stimuli when the deviants consisted of the single bar and the standards consisted of the double bar.

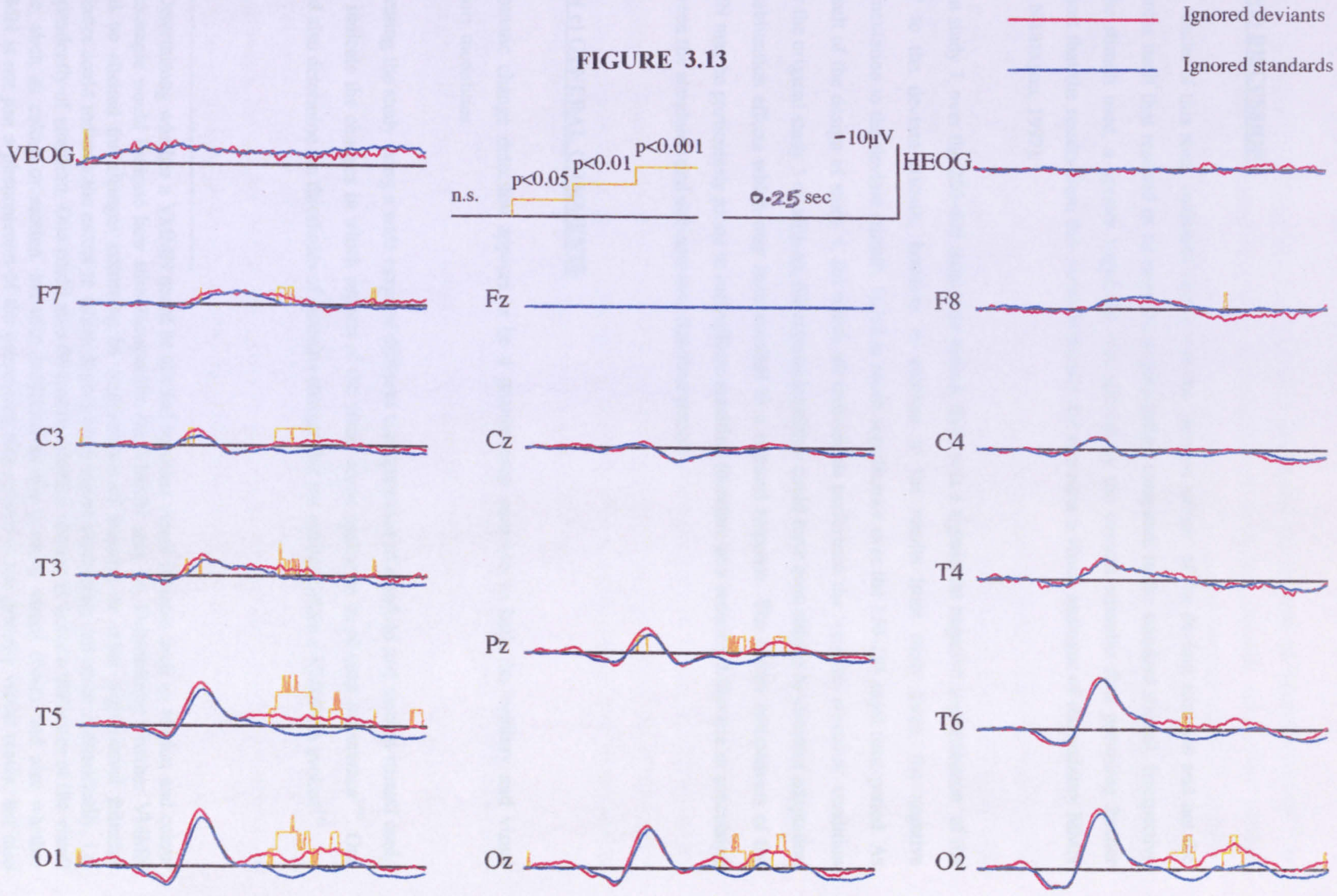
The results clearly indicated a greater negativity to the deviant compared to the standard stimuli even though it was the single bar that formed the deviant stimuli. The form, amplitude and latencies for this configuration of standard and deviant stimuli were very similar to those in study three.

The mean difference in negativity between the deviant and standard stimuli over the 150-280msec and 280 to 400 msec periods of time was measured and the results displayed in table A3.5 of the chapter 3 appendix. A paired t-test was then applied to the difference data for each time period and resulted in the following findings:

The enhanced negativity to the deviant stimuli over the 150-280 msec time period failed to reach significance at T5, t (df 11) = 0.96, $p > 0.05$; T6 t (df 11) = 0.9, $p > 0.05$. O1, t (df 11) = 1.04, $p > 0.05$; O2, t (df 11) = 0.94; Oz, t (df 11) = 0.5, $p > 0.05$.

The enhanced negativity to the deviant stimuli over the 280-400msec time period, did however reach significance at T5 t (df 11) = 3.23, $p < 0.05$; T6 t (df 11) = 2.28 $p < 0.05$; O1, t (df 11) = 3.29, $p < 0.05$; O2, t (df 11) = 2.92, $p < 0.05$ and Oz t (df 11) = 2.4, $p < 0.05$,

FIGURE 3.13


Ignored deviants
Ignored standards
VEOG
HEOG
n.s.
p<0.05
p<0.01
p<0.001
−10μV
0·25 sec
F7
Fz
F8
C3
Cz
C4
T3
T4
Pz
T5
T6
O1
Oz
O2

3.30(b) DISCUSSION

The results of this study indicated that it was the 'deviant nature' of the deviant stimulus and not the stimulus itself that resulted in its negative augmentation compared to the standard stimuli. Irrespective of the stimuli used, a greater negativity was elicited by the deviant stimulus thus providing further support that the results from this series of studies did represent a visual analogue of the auditory MMN (see Näätänen, 1992).

As in study 3, over the 280-400 msec time period, there was a significant negative augmentation of the ERP to the deviant stimuli; however in contrast to the results from study three, the negative augmentation to the deviant stimuli, failed to reach significance over the 150-280 msec time period. As a result of the design of study 4, (in which all individuals performed the 'reverse- stimulus' condition after the original study 3 condition), the reverse condition could have been subject to stimulus adaptation or habituation effects which may have resulted in a reduced response. The earlier components of the MMN may be particularly prone to such effects resulting therefore in a reduced difference in processing between the standards and deviants over this time period.

3.30(c) GENERAL COMMENTS

Automatic change detection appears to be a phenomenon common to both the auditory and visual sensory modalities.

Repeating the study using a wide range of different configurations of standard and deviant stimuli could also indicate the changes in which aspects of the visual scene appear to be of most importance[140]. One could also determine the thresholds of stimulus change that are needed before a VMMN is evoked[141].

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[140] Determining whether a VMMN could be elicited by other visual features such as motion and colour for example would indicate how stimulus-specific the VMMN may be. Determining whether VMMN could be elicited for changes occurring in conjunctions of features or other higher-level stimulus attributes could indicate the extent to which higher level visual processing can occur automatically, i.e. independently of attention. One could also determine whether change in certain attributes of the visual scene, such as colour or motion, are also mediated by the primary visual cortex and also whether VMMN is not just a phenomenon of the processing that occurs in the primary visual cortex, but also whether such mechanisms also occur in the extrastriate areas. Such studies have been performed in the auditory modality, see section 3.11(A).

[141] Several further studies could be performed to determine in greater detail the similarity between the visual and auditory MMN; for example manipulating the ISI, deviant probability and similarity of standards and deviants (see section 3.12). The effects of sensory adaptation could be further determined by presenting the stimuli continuously for longer periods of time.

Further studies of VMMN are also required which manipulate the strength of focused attention[142] to determine whether, although apparently independent of attention, attention can, under certain circumstances, modulate such processing (which appears to be the case in auditory MMN)[143]. Another important aspect of the VMMN would be to determine whether (as suggested for the auditory MMN, see section 3.11 (B)) it serves to cause a shift in attention to previously unattended stimuli. Such experiments were however beyond the remit of the present study.

The finding of a visual mismatch negativity in healthy young adults provided a potential technique for the study of early attention-independent visual processing in older adults and individuals with Alzheimer's disease.

3.31 STUDY 5 AGEING AND THE VISUAL MISMATCH NEGATIVITY

The findings from the majority of neuropathological and neuroimaging studies (described in chapters one and two) have indicated that the occipital cortex, particularly the striate region, is relatively spared in ageing[144]. However the results from VEP studies in ageing had tended to show an increase in the latency of the P100 component of the pattern reversal VEP[145] with increasing age, indicating therefore that some age-related deficits in occipital cortex processing did occur.

The prediction of the present study was therefore that although a VMMN would be evoked in older adults it would be impaired in comparison with that evoked in young adults.

The design of the stimuli used to elicit the VMMN in study three (i.e., the requirement to fixate centrally and to detect and respond to the centrally presented red target) was intended to make the task both easy to understand and to perform. By avoiding the need for complex instructions and performance requirements, the possible confounding factors resulting from memory and cognitive impairment that can be found in both older adults and individuals with Alzheimer's disease, was reduced..

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[142] For example, by making the target task to which the participant has to attend to in the central square even harder. This could be achieved by using a discrimination rather than a detection task, thereby drawing attention even more strongly away from the 'supposed' non-attend area surrounding the central square in which the standard and deviant stimuli are presented.

[143] Because of the parallel processing component inherent in visual processing it would be interesting to determine whether automatic change detection in several different physical features could also occur in parallel. Rather than there being a 'single' change detection mechanism that registers change in the visual scene as a whole there could be many VMMN mechanisms, tuned to specific aspects of the visual environment such as colour and motion, that can work in parallel.

[144] Compared to the areas of the brain involved in higher level processing (such as the parietal and temporal cortices).

[145] (also thought to be the result of processing in the striate cortex)

3.31(a) PARTICIPANTS.

A group of 12 older adults (8 female, 4 male) age range, 69 to 88, mean 77 years, was compared to the group of 12 young adults who took part in study 3 (8 female; 4 male, age range 24-43, mean age 32 years). The older adult group were recruited from the 'BRACE' Centre Memory Clinic[146] healthy volunteer panel (i.e., non-dementing and no other neurological disorders). All participants had normal or corrected to normal vision; both verbal and written consent was obtained from all participants and no payment was given for participating. The individuals in the older adult group were all within normal age-related cognitive measures, for example exhibited 28 or above, on the MMSE scale[147].

STIMULI

The stimuli and experimental procedure used were identical to those used in study three.

EEG RECORDING PARAMETERS

The EEG recording and set up parameters were also identical to those used in study three.

3.31(b) RESULTS

Figure 3.14 illustrates the event related potentials, referenced to Fz, elicited to the non-attended standard and deviant stimuli for the group of 12 older adults.

The ERPs of the older adults to the standard and deviant stimuli resembled those evoked by the younger adults. There were however some differences. For example, at O1 and O2, the first negative component had a peak latency of 190 msec compared to a latency of 175 msec for the younger adults, representing a delay in latency for the older adults. The ascending limb of this negative component was also different in form to that of the young adults, having an additional small negative peak at approximately 140 msec. Also in comparison to the young adults, there was a much reduced negative enhancement of the deviants compared to the standards over the later part of the ERP, starting at approximately 278 msec. Similar changes were also apparent at T5 and T6.

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[146] Based at Blackberrry Hill Hospital, Bristol.

[147] MMSE = mini-mental state examination; is not a diagnostic instrument, but is used as a method of assessing the severity of cognitive impairment (see McKeith 1997 for a review). On the MMSE scale a score of 27-30 = normal; 25-26 = possible dementia; 10-24 = mild-moderate dementia and < 6 = severe dementia.

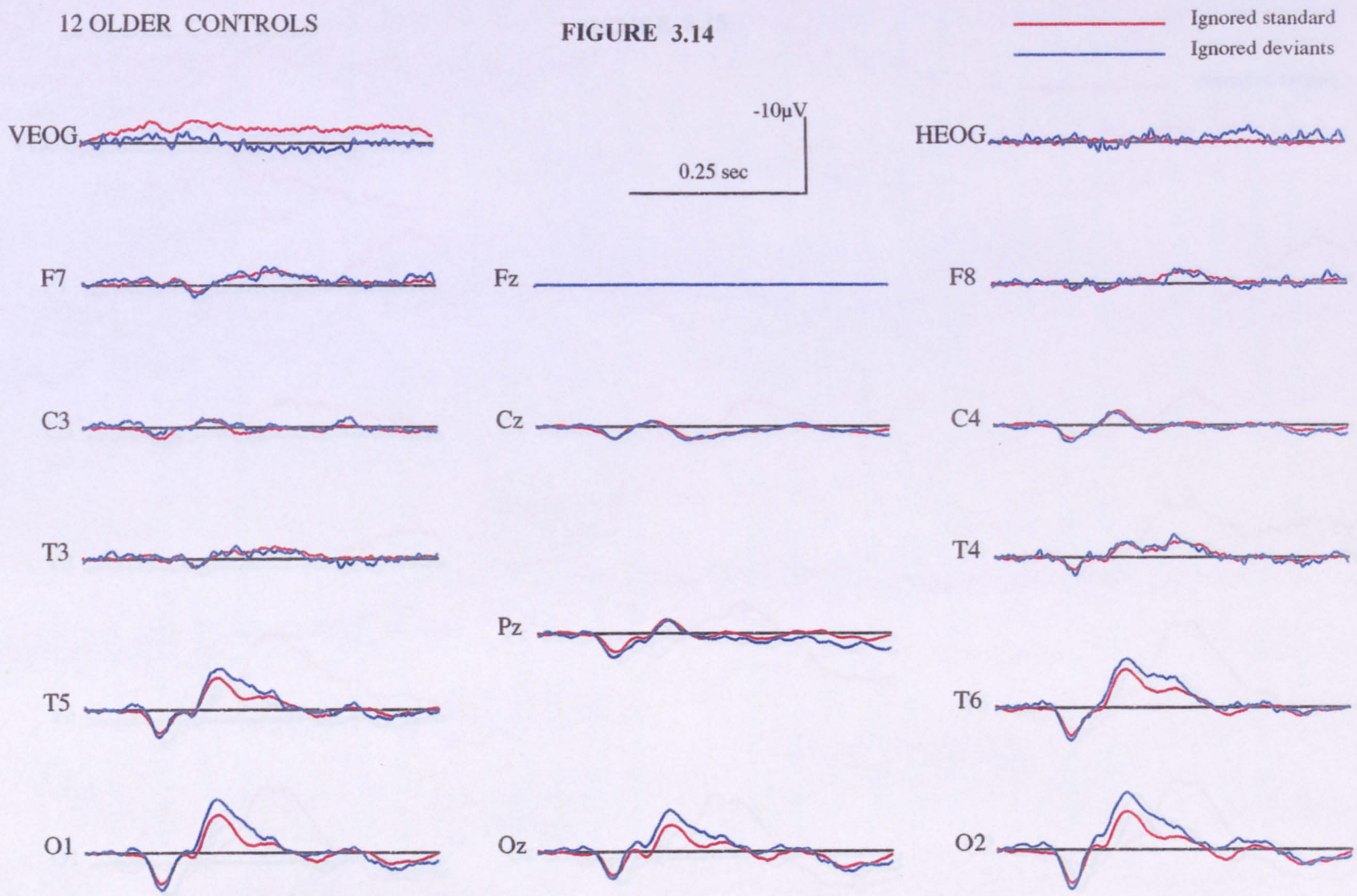
For the posterior electrode sites, (T5, T6, O1, Oz, O2) the mean difference in negativity between the deviant and standard stimuli over two different periods of time, 150-280msec and 280 to 400 msec, was measured; the results are displayed in table A3.6 of the chapter 3 appendix. A paired t-test was then applied to the difference data for each time period and resulted in the following findings:

Over the 150 - 280 msec time period although the enhanced negativity to the deviant stimuli failed to reach significance at T5, t (df 11) = 1.48, $p > 0.05$; it did reach significance at T6, t (df 11) = 3.3, $p < 0.01$; O1, (df 11) =2.53,, p <;0.05; O2, (df 11) = 3.48, $p < 0.01$ and Oz, (df 11), 2.5, $p < 0.05$. So as was the case for younger adults, ageing was accompanied by a significantly greater negativity of the ERP to the deviant compared to the standard stimuli over the early part of the MMN.

However, the enhanced negativity to the deviant stimuli over the 280 - 400 msec time period failed to reach significance. T5, t (df 11) = 0.17, $p > 0.05$; at T6, t (df 11) = 0.64, $p > 0.05$; at O1, (df 11) = 0.52, $p > 0.05$; at O2, (df 11) = 1.35, $p > 0.05$ or at Oz, t (df 11) = 0.88. This was not the case for young adults.

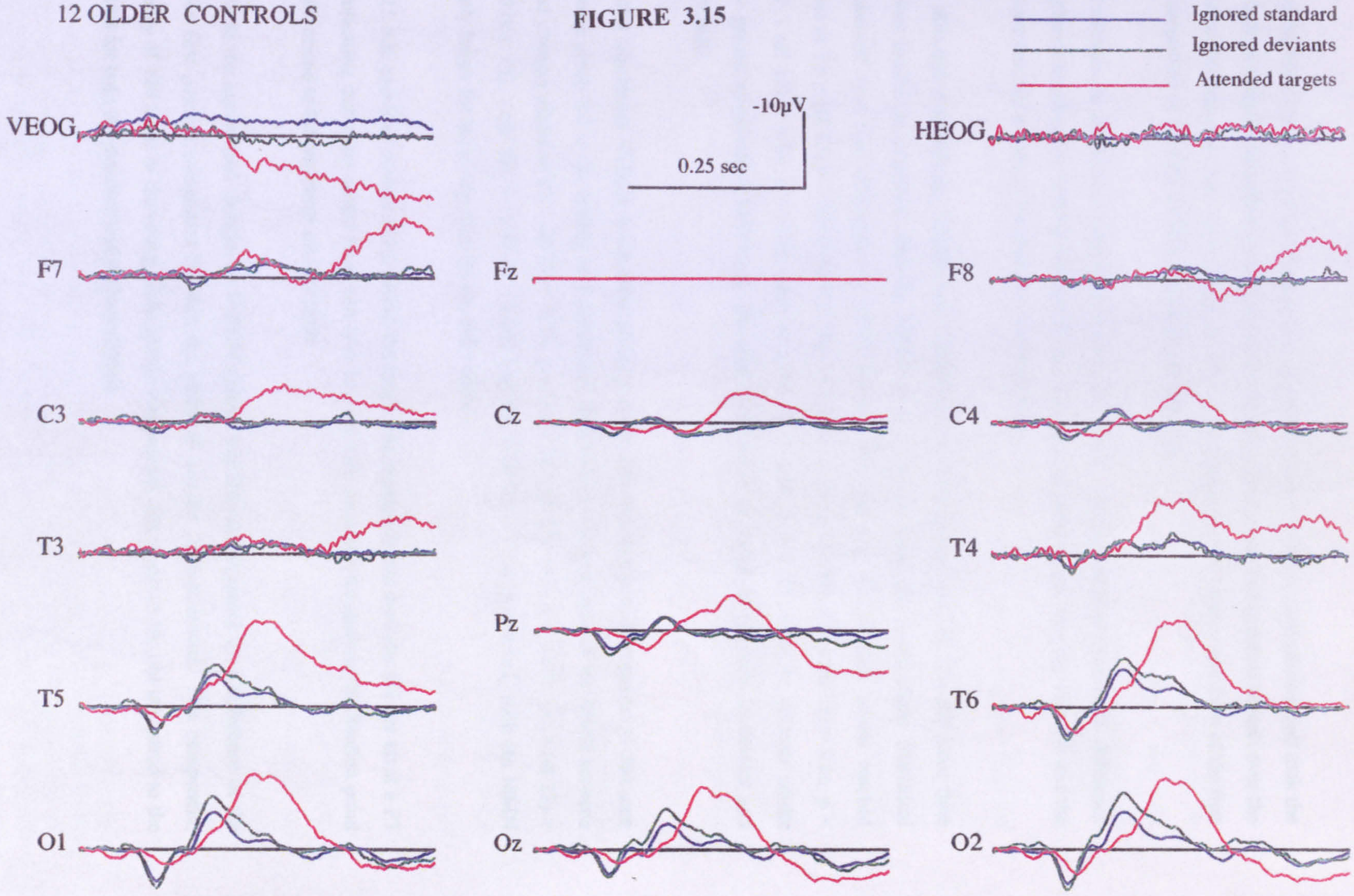
12 OLDER CONTROLS

FIGURE 3.14



12 OLDER CONTROLS

FIGURE 3.15



Ageing did therefore appear to be accompanied by an impairment in VMMN, as predicted, and took the form of a lack of a significant difference in negativity between the deviant and standard stimuli over the later period of the response. Age-related changes were also apparent in the latency and form of the first negative component of the ERP to both standards and deviants.

Statistical analysis, in the form of independent measures t tests, was applied to determine the difference in the amplitude between the VMMN elicited by the younger and older adults over the 150-280 and the 280-400 msec periods of time at the posterior electrode sites.

However, although a significant VMMN was elicited by the older group over the 150-280 msec time period it was smaller in amplitude than the difference in negativity found for young adults. Statistical analysis showed that this difference in MMN between the old and the younger adults reached significance at T5, t (df 22) = 7.86, $p < 0.001$; T6, t (df 22) = 7.25, $p < 0.001$; O1, t (df 22),= 9.16, $p < 0.001$; O2, t (df 22) = 9.19, $p < 0.001$ and Oz, t (df 22) = 6.60, $p < 0.001$, with the younger adults having the greater amplitude of MMN (i.e., the greater difference in negativity between the deviant and standard stimuli.

The lack of a significant VMMN in the older group over the 280-400msec period compared to that seen for the young group led to the finding of a significant difference in the amplitude of the MMN between the old and younger adults at T5, t (df 22) = 2.16, $p < 0.05$; T6 t (df 22) =5.2, $p < 0.001$; O1, t (df 22) = 6.0, $p < 0.001$; O2, t (df 22) = 11.92, $p < 0.001$ and Oz, t (df 22) = 7.26, $p < 0.001$, with the MMN significantly larger for the young than for the older adults.

Figure 3.15 also provides evidence that unlike the target, the standards and deviants did not elicit a P3 or P3b, indicating that older adults were also able to keep their attention focused on the fixation point and did not attend to the standards and deviants.

In addition to the age-related changes in VMMN ageing was also accompanied by a difference in the form of the first positive component for both the standard and the deviant stimuli. This component, (peak latency of 120 msec in the young adult group) was sharper and larger in the old compared to the young adults for both the standard and deviant stimuli.

3.32 DISCUSSION OF THE RESULTS

As proposed, visual VMMN although present in older adults was reduced in amplitude compared to younger adults. The results of the present study therefore provided evidence, in addition to that from VEP studies, that the occipital cortex, in particular the striate cortex although spared relative to other higher levels of visual processing in ageing, still suffers from some age-related decrement in function.

The reasons behind the age-related reduction in amplitude of VMMN were not apparent from the present results. If however, as Näätänen (1992) suggests, the neuronal representations of auditory stimuli are laid down in an echoic or sensory-memory, which becomes less efficient with increasing age[148], then the results pertaining to Visual MMN may be the consequence of a similar age-related decrement in the processes underlying visual sensory memory or neuronal trace production.

The reduced visual MMN during the earlier ERP period may have led to a reduction in the significance allotted to the deviant stimulus by the subsequent later-stages of visual processing, resulting in a reduction in the amplitude of the associated ERP over the 280-400msec time period[149].

Pekkonen et al., (1993) found that involuntary attention switching to auditory stimuli was less efficient with ageing; it would be useful to determine whether this is also the case in the visual modality. Behavioural evidence already exists that a reduction in the salience of a visual target results in a reduced efficiency of shifting attention to it [150]. It may be the case that a reduction in the saliency of the difference between standards and deviants, as appears to happen in ageing, may result in a reduction of the ability of this 'change' to attract attention and consequently affect behaviour.

The finding of a reduction in the efficiency of early automatic visual processing as evinced by the reduction in amplitude of the VMMN in ageing may also indicate that the age-related deficits in the later stages of visual processing may not be due simply to changes in the areas of the brain underlying the higher level visual processes but also to dysfunction at the earlier stages; a consequence of which could be a reduction in appropriate information reaching its destination.

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[148] In terms of auditory MMN and ageing, Pekkonen et al. (1993) found that auditory MMN to duration and frequency change was stable regardless of age with short ISIs (i.e.,1 sec); and as suggested by the authors, indicated that automatic stimulus change detection per se was not impaired by ageing. However, they did find evidence that with a 3 sec, ISI, the MMN was significantly smaller with ageing and suggested that this may reflect the shortening of sensory memory trace with increasing age.

[149] The apparently impaired stimulus change detection as illustrated by the reduced VMMN observed in older adults may have important consequences for their everyday behaviour such as driving a car; a process which relies heavily on our ability to detect and react automatically to changes going on in the environment.

The differences in the first positive ERP component to both the standard and deviant stimuli in ageing may also have been an indication of changes in early visual processing which may well have consequences for the later stages of visual processing.

3.33 STUDY 6 ALZHEIMER'S DISEASE AND VISUAL MISMATCH NEGATIVITY

Study 5 indicated that as predicted, ageing detrimentally affected VMMN production, probably as a result of age-related changes to the occipital cortex. According to the majority of neuroimaging studies, Alzheimer's disease resembled normal ageing in that the occipital cortex was spared in relation to the areas of the brain involved in higher-level visual processing, with many studies reporting few or no significant differences in occipital function between ageing and AD. This together with the findings that in AD, the P100 remained relatively unchanged compared to normal ageing (e.g. Philpot et al., 1990; Sloan and Fenton, 1992) lead to the general idea that the occipital cortex and in particular the striate cortex was spared in AD and consequently that automatic visual processing, a product of the visual processing in this area, should also be spared in AD.

If indeed the occipital cortex were spared in AD then one would expect to find a preserved VMMN, the result of automatic visual processing, in relation to that seen in normal ageing. The aim of study 6 was to determine whether this was the case.

3.33(a) PARTICIPANTS

Eight individuals with NINCDS-ADRADA-diagnosed probable Alzheimer's disease took part, all females. Their ages ranged from 53 to 90 the mean being 78 years. The mean score on the MMSE was 24. The older adult group consisted of 8 age-matched controls (taken from the older adult group in study 5); their ages ranged from 69 to 88, with a mean of 79 years.

All the older adults and older adults with AD, were recruited from the BRACE centre memory clinic, all were drug free. The individuals with AD had also been recruited for a major drug trial which was to begin after they were tested in the present study. The older adults had taken part in previous non-drug-related research. All had normal or corrected to normal vision. The individuals with AD had all presented with a typical onset. Written and verbal informed consent was obtained from each participant and their carer if appropriate, after a full explanation of the study had been given.

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[150] [when individuals are cued to a target (Brawn and Snowden submitted, 1998; personal communication, Snowden, 1998].

The results of the young adult group were taken from the results of the first 8 individuals who performed the study 3; mean age, 28 years. The results of the old adult group were the results of a subset of the original 12 adults who were matched for age to those with AD.

STIMULI

The stimuli and experimental procedure used were identical to those used in study three. (Except that more breaks were given and the task instructions were repeated numerous times at intervals throughout the duration of the recording. In the case of individuals with AD, their carer was also in the recording room).

3.33(b) RESULTS

Figure 3.16; 3.17 and 3.18, illustrate the ERP to the standard and deviant stimuli for the young; older adult and AD group respectively.

For the posterior electrode sites (T5, T6, O1, Oz and O2) the mean difference in negativity between the deviant and standard stimuli over two different periods of time, 150-280msec and 280 to 400 msec, was measured for the young adult, the older adult and the AD group; (the results are displayed in table A3.7, A3.8 and A 3.9 respectively, of the chapter 3 appendix). A paired t-test was then applied to the difference data for each time period and resulted in the following findings:

FIGURE 3.16 (8S).

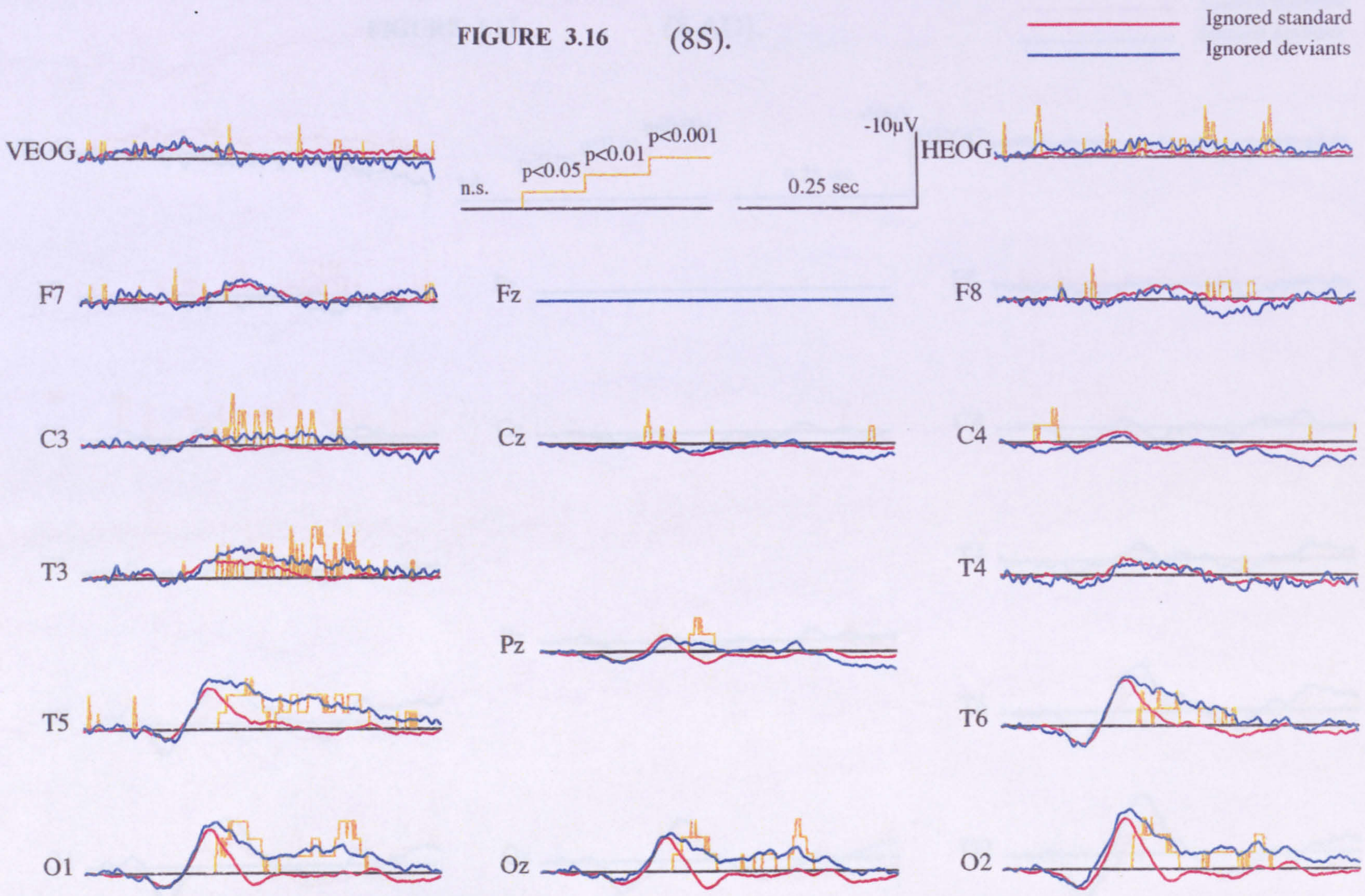


FIGURE 3.17 (8 AD).

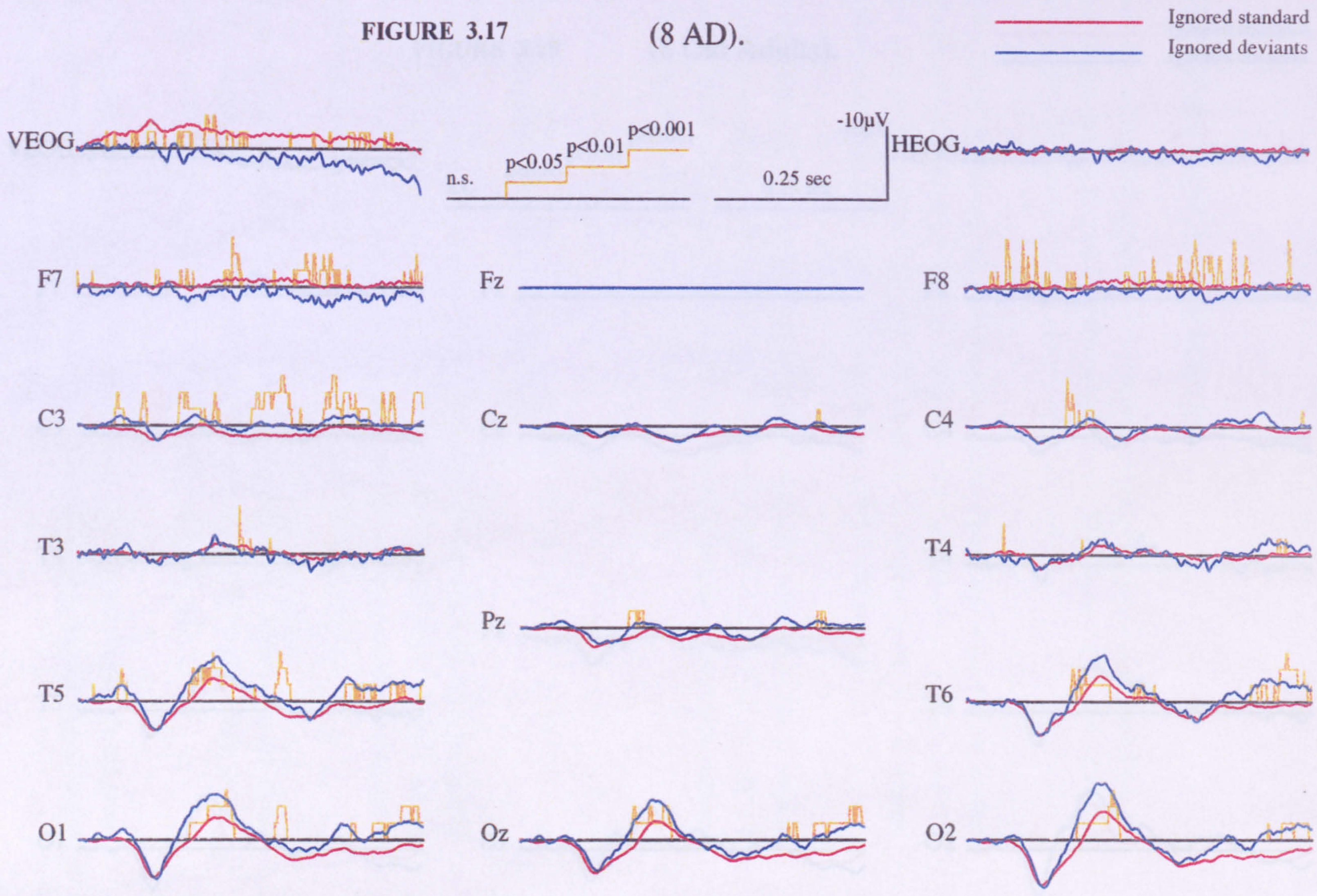
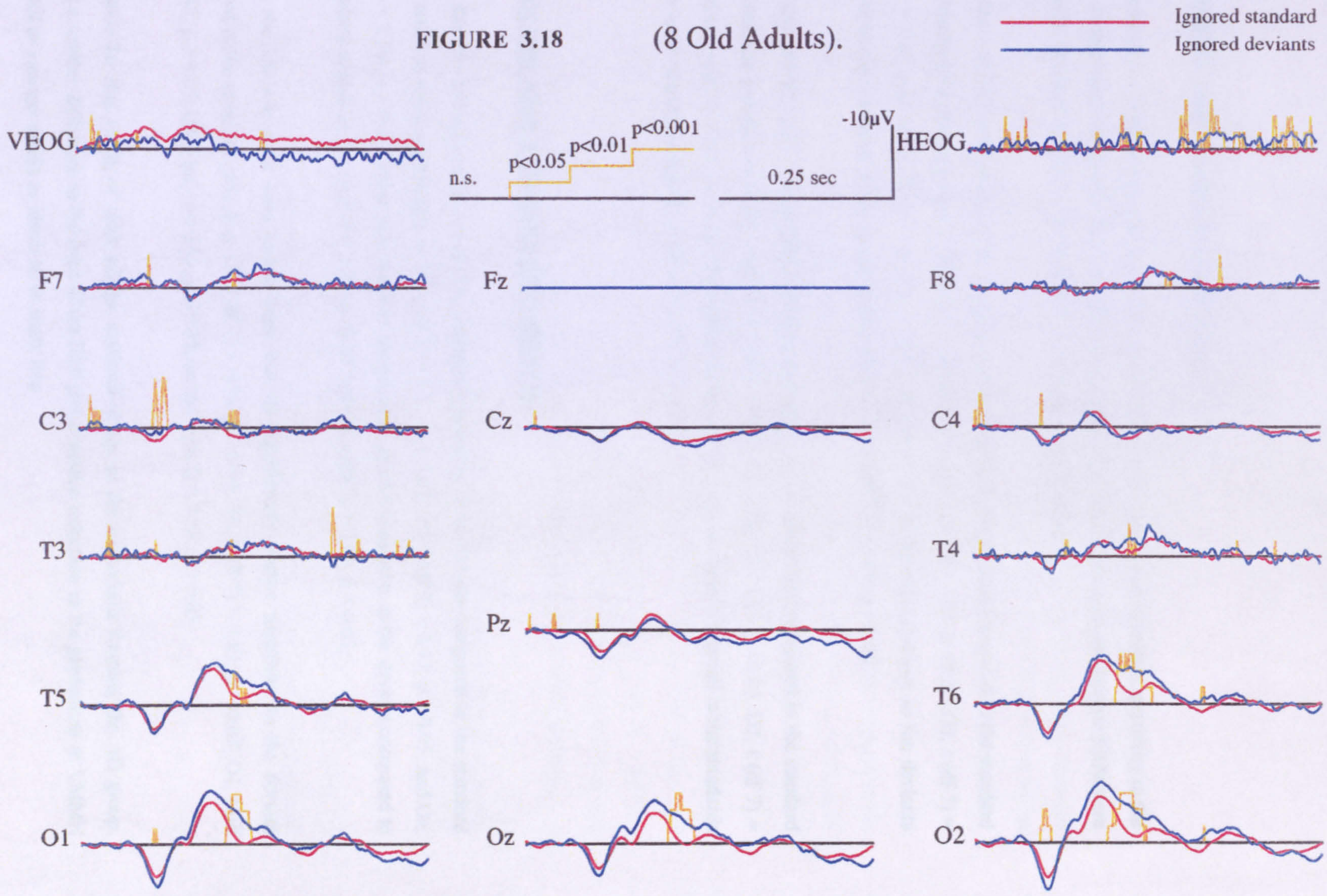


FIGURE 3.18 (8 Old Adults).



3.34 8 YOUNG ADULT GROUP VMMN RESULTS.

The results of the young adult group were characterised by a very prominent enhanced negativity to the deviant compared to the standard stimuli. The form and latencies of the standard and deviant ERPs were very similar to those evoked in the 12 young adult group of study three.

During the 150-280 msec time period, the enhanced negativity of the deviant compared to the standard stimuli reached significance, at T5, t (df 7) = 3.10, $p < 0.02$; O1, t (df 7) = 3.54, $p < 0.01$; O2, t (df 7) = 2.78, $p < 0.05$ and Oz, t (df 7) = 2.62, $p < 0.05$. However, the enhanced negativity to the deviants compared to the standards at T6, failed to reach significance, t (df 7) = 2.05, $p > 0.05$.

During the 280-400 msec time period, the enhanced negativity of the deviant compared to the standard stimuli reached significance at T5, t (df 7) = 3.48 $p < 0.02$; O1, t (df 7) = 3.87, $p < 0.01$, O2, t (df 7) = 2.68 and Oz, t (df 7) = 2.9, $p < 0.02$. The enhanced negativity to the deviants compared to the standards failed to reach significance at T6, t (df 7) = 1.96, $p > 0.05$.

3.35 8 OLDER ADULT GROUP VMMN RESULTS

During the 150-280 msec time period, the enhanced negativity of the deviant compared to the standard stimuli failed to reach significance at T5, t (df 7) = 1.21, $p > 0.05$; O1, t (df 7) = 2.17, $p > 0.05$; and Oz, t (df 7) = 2.24, $p > 0.05$. There was however significantly greater negativity to the deviant compared to the standard stimuli at T6, t (df 7) = 2.75, $p < 0.05$ and O2, t (df 7) = 2.75, $p < 0.05$.

During the 280-400 msec time period there was no significantly greater negativity to the deviant compared to the standard stimuli at T5, t (df 7) = 0.13, $p > 0.05$; T6, t (df 7) = 0.83, $p > 0.05$; O1, t (df 7) = 0.42, $p > 0.05$; O2, t (df 7) = 0.91, $p > 0.05$, or Oz, t (df 7) = 0.68, $p > 0.05$.

The results for this subset of older adults, matched in age to the individuals forming the AD group, showed a similar difference in the form of the ERP and a similar reduction in the production of VMMN compared to younger adults as observed in study five.

3.36 AD GROUP MISMATCH NEGATIVITY

The ERPs of the AD group to the deviant and standard stimuli resembled a mixture of those for the young and older adult groups. Like the older adult group, the ERP for the AD group, for both the deviant and standard stimuli, was characterised by a prominent, sharp P120 component at the posterior electrode sites. Unlike the older group however, the ERPs of the AD group were characterised by an enhanced negativity to the deviant stimuli over both the 150-280 and the 280-400 msec periods of time; the amplitude of this negative enhancement resembled that which occurred in the young adult group.

During the 150-280 msec time period the enhanced negativity of the ERP to the deviant compared to the standard stimuli reached significance at T5 t (df 7) = 3.35, $p < 0.02$; at 01 t (df 7) = 2.97, $p < 0.05$, at 0z t (df 7) = 2.39, $P < 0.05$; at 02 t (df 7) = 3.19, $p < 0.02$; and at T6 t (df 7) = 3.14, $p < 0.02$.

However, during the 280-400 msec time period, the negative enhancement of the ERP to the deviant compared to the standard stimuli failed to reach significance at T5 t (df 7) = 1.45, $p > 0.05$; at 01, t (df 7) = 1.53, $p > 0.05$; at 0z, t (df 7) = 1.06, $p > 0.05$; at 02, t (df 7) = 0.77, $p > 0.05$; or at T6 t (df 7) = 0.67. So although there appeared to be a substantial difference between the ERPs to the standard and deviant stimuli and therefore a large VMMN component, this difference failed to reach significance.

In addition, the latency of the major negative component was delayed in AD compared to normal ageing (N205 msec compared to N175msec respectively) and slightly reduced in amplitude in AD compared to normal ageing. These differences were best seen at both O1 and O2.

The effects of AD therefore appeared to closely resemble those found in normal ageing. Table 3.1 illustrates the patter of the enhanced negativity to deviant stimuli over the two periods of time measured in the present study.

Table 3.1

	Comparing the negativity of the ERPs to the deviant compared to the standard stimuli	
	150-280 msec	280-400msec
Young Adults	Significantly greater except at T6	Significantly greater except T6
Older Adults	Only significant difference at O2 and T6	No significant difference
Older adults with AD	Significantly greater	No significant difference

The results of the young adult, older adult and AD groups showed that a significant VMMN was evoked for all three groups over the 150-280 msec time period. However, unlike the young adult group, both the older adult and AD groups failed to produce a significant MMN over the 280-400msec time period.

3.37 COMPARING THE AMPLITUDE OF THE VMMN IN AGEING AND AD

Statistical analysis, (independent measures t tests) were then employed to determine the difference in the amplitude between the VMMN elicited by the younger and older adults and the older and older adults with AD over the 150-280 and the 280-400 msec epochs at these electrode sites.

3.38 COMPARING THE 8 YOUNG AND 8 OLDER ADULTS

The mean difference in VMMN between the 8 young and the 8 older adults is presented in table A3.11 of the chapter 3 appendix.

Over the period 150-280 msec there was a significant difference in MMN amplitude between the young and older adults, at T5, t (df 14) = 3.82, $p < 0.01$; O1, t (df 14) =2.5, $p < 0.05$; O2, t (df 14) = 2.52, $p < 0.05$, with the younger adults having the greater amplitude. There was no significant difference in VMMN amplitude between the young and older adults at T6, t (df 14) = 1.69, $p > 0.05$ or Oz, t (df 14) = 1.07, $p > 0.05$.

Over the period 280-400msec there was no significant difference in MMN amplitude between the young and the older adults at T5, t (df 14) = 1.24, $p > 0.05$; there was however a significant difference in VMMN between the young and older adults for T6, t (df 14) = 2.58, $p < 0.05$; O1, t (df 14) = 3.09, $p < 0.01$; O2, t (df 14) = 4.65, $p < 0.001$ and Oz, t (df 14) = 3.3, $p < 0.01$, with the younger adults having

the greater MMN. The results therefore show an age-related decrement in the amplitude of VMMN produced at this period of time.

3.39 COMPARING THE 8 OLDER ADULTS WITH THE 8 ADULTS WITH ALZHEIMER'S DISEASE

A table showing the mean difference in VMMN between the older adults and the older adults with AD is in table A3.12 of the chapter 3 appendix.

Over the period 150-280 msec, there was a significant difference in MMN amplitude between the old and AD groups at T5, t (df 14) = 2.57, $P < 0.05$; with the greater MMN for AD. There was however no significant difference at T6, t (df 14) = 1.34, $p > 0.05$; O1, t (df 14) = 1.37, $p > 0.05$; O2, t (df 14) =0.79, $p > 0.05$ or Oz, t (df 14) = 0.29, $p > 0.05$.

Over the period 280-400 msec, there was no significant difference in MMN amplitude between old and AD group, T5 t (df 14) = 0.51, $p > 0.05$; T6, t (df 14) = 0.06, $p > 0.05$; O1, t (df 14) = 1.51, $p > 0.05$; O2, t (df 14) = 0.39, $p > 0.05$; or Oz, t (df 14) = 0.9, $p > 0.05$.

The results therefore appeared to suggest that individuals with AD appeared to suffer no further decrement in VMMN compared to that found in normal ageing. In fact, although largely not reaching significance, the individuals with AD appeared to have a greater VMMN than the older adults. The results could therefore have been interpreted as indicating that automatic visual processing (at least that indicated by VMMN) was spared in AD relative to the normal age-related deficits.

However, the finding that the amplitude was in fact larger for the VMMN in AD compared to older adults throughout the trace led to the closer inspection of the traces for both older and AD adults.

For all three groups of individuals the deviant and standard stimuli traces were compared. These can be seen in figure 3.19.

FIGURE 3.19

RESPONSES TO IGNORED DEVIANT STIMULI.

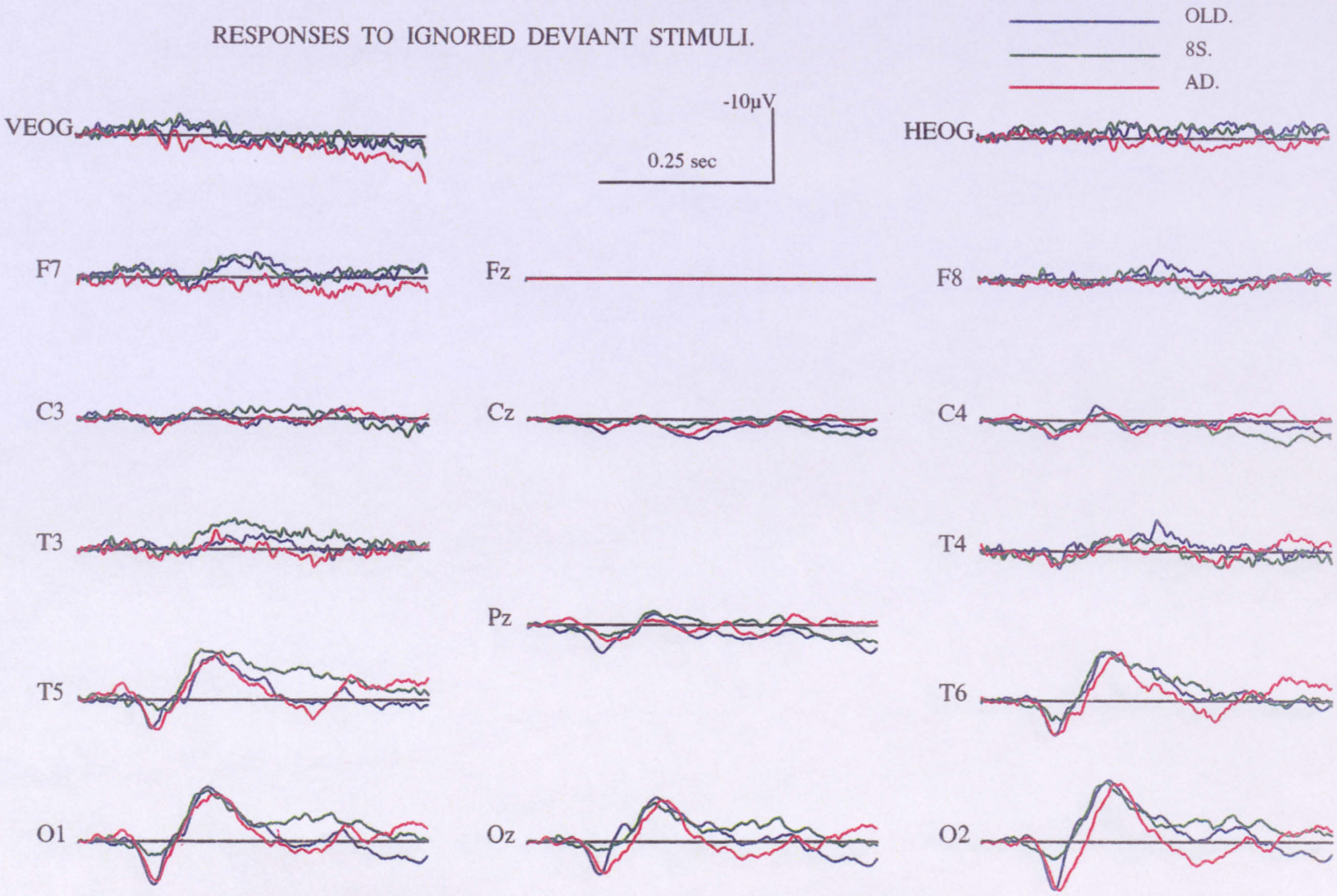
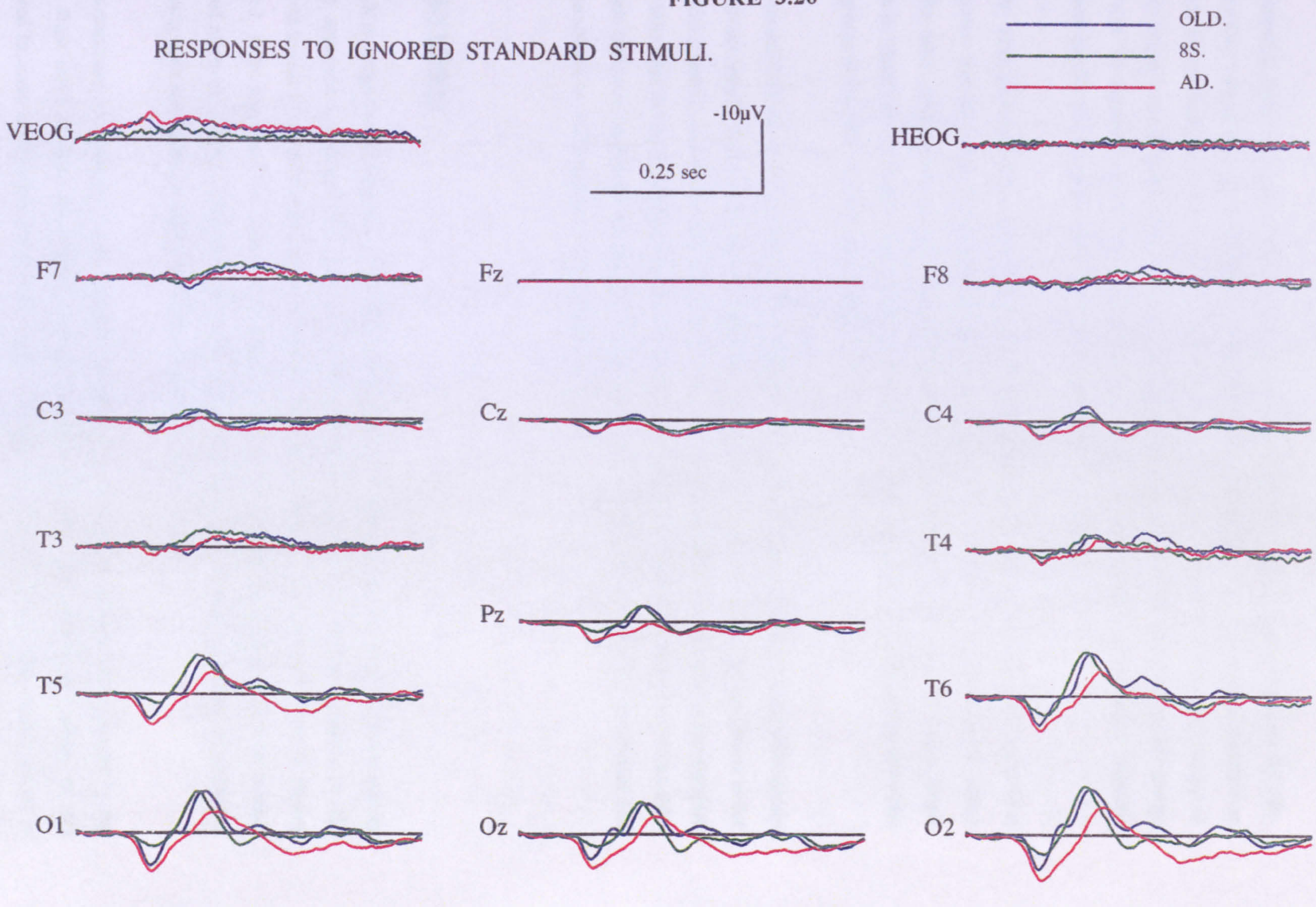


FIGURE 3.20

RESPONSES TO IGNORED STANDARD STIMULI.



As illustrated in figure 3.19, at O1 and T5 and O2 and T6, the ERP to the deviant stimuli over the 150-280 msec time period was very similar in both form for all three groups. There was a small reduction in amplitude for the AD compared to the young and older adult groups. At O1 and T5 the peak latency of the major negative component was similar for the three groups, but with a slight delay for the AD group. At O2 and T6 however, there was a much larger increase in the latency of the major negative component for the AD group compared to both the young and older adult groups.

However, when one studied the traces to the standard stimuli in figure 3.20, O1and T5 and O2 and T6 it was apparent that the reduction in amplitude and increases in latency for the AD compared to the young and older adult groups were greater than those seen for the deviant stimuli. The was also a larger increase in latency of the major negative component for the AD group compared to the young and older adults groups at O2 and T6 than at O1 and T5.

The enhanced VMMN over the 150-280 msec time period for the AD compared to the older adult group (although not significantly so) appeared therefore to have been the result of the reduced amplitude of the ERP to the standard stimuli in AD. Because the AD group had a smaller ERP amplitude to the standard stimuli than that for the older adult group, the result of subtracting the standards from the deviant ERP amplitude (that was similar for both groups) would result in a greater difference between the deviant and standard stimuli in AD compared to the older adult group.

3.40 DISCUSSION

The lack of a significant reduction in VMMN amplitude in AD compared to that seen in normal ageing initially appeared to indicate that there was no greater deficit in automatic visual processing in AD compared to that found in normal ageing. However, the finding that the processing of standard stimuli appeared to be abnormal, i.e., reduced in amplitude, in AD, while the processing of deviant stimuli appeared relatively normal compared to normal ageing, suggested that in fact some aspects of automatic processing were detrimentally affected in AD compared to normal ageing.

This impairment of automatic visual stimulus processing would suggest therefore that contrary to the results from other studies, the occipital cortex, although relatively spared from the effects of AD compared to many other brain areas, does in fact suffer some functional decrement. Such a deficit in even the most basic visual processing in AD may affect the flow and quality of information reaching the areas of the brain associated with higher-level visual processing. This could therefore have consequences for the efficiency of higher level visual processing and indeed may even affect memory processes; (i.e., if a stimulus has not been properly registered and processed at an early level then it may not be able to

enter memory. such problems may result in the common failure of new memory formation in AD). Further research is of course necessary to determine whether this may indeed be the case.

Although further research is required to determine whether the effects of AD on VMMN are robust some suggestions can be proffered as to their underlying cause. For example it may the case that in AD, there is greater habituation (sensory fatigue) or inhibition of responses to a stimulus that is repeatedly presented (i.e., the standard stimulus), therefore causing a reduction in the amplitude of its associated ERP response compared to that which occurs in ageing alone[151].

The effects of sensory fatigue could be determined in future studies by comparing ERPs elicited in response to the standard stimuli at the beginning and end of the recording. A reduction in the amplitude of the standard ERP over time would suggest sensory habituation to the standard stimuli. The lack of a reduction in amplitude of the standard ERP over time, could indicate instead that the reduction in AD could be the result of a generalised inhibition of responses rather than sensory habituation.

To determine whether there is greater inhibition to visual stimuli in AD than in ageing a test which measures inhibition, (or selective adaptation) of visual neurons, such as the tilt or motion after effect could be employed. Indeed this technique has already been used to study occipital cortex-related visual function in Parkinson's disease. Calvert et al. (1990; 1992) found a reduction in the magnitude of the tilt after effect in Parkinson's disease. This result was interpreted by the authors as indicating reduced inhibition to visual stimuli in PD[152]. If it is the case in Alzheimer's disease that 'too much' inhibition occurs in response to commonly presented visual stimuli then individuals with AD may also produce a tilt after effect of greater magnitude than that found in older adults. Of course some inhibition of response is required to enable one to focus on a specific aspect of the environment. Too much inhibition however, could have consequences for behaviour, in that relevant information is prevented from being processed adequately.

It might be the case that the ERP to the deviant stimuli in AD appeared normal because the deviant stimuli were presented rarely and were therefore less likely to suffer from the effects of sensory fatigue or inhibition which occur to commonly presented stimuli.

It has also been proposed by several researchers (see Desimone, Chelazzi, Miller and Duncan, 1995 for a review), that a mechanism called adaptive filtering occurs in the brain. In this mechanism incoming

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[151] The AD-related decrease in acetylcholine, an excitatory neurotransmitter (see section 1.8) may also cause changes in excitation and inhibition to visual stimuli, dependent perhaps on how often they are presented over a period of time. See also Desimone and Duncan's, 1995 'suppressive mechanism' based on stimulus repetition, section 3.25 which could perhaps be altered by AD.

[152] The greater the tilt after effect the greater the inhibition or selective adaptation of the neurons involved.

sensory information is filtered by neurons according to how similar it is to information already held in either short or long term memory. They describe how in monkeys for example, some of the neurons in IT cortex that respond selectively to particular object features, such as specific colour or shape, give their best responses to objects that contain those features but that are new, unexpected or not recently seen. As new stimuli become familiar, synaptic weights in the cortex appear to adjust so that the neuronal response is dampened[153]. A similar filter, perhaps based on the early neuronal representations of simple stimuli, could occur in the occipital cortex in order to filter out lower level attributes that become familiar. If this were the case, then an affect of AD could be an over-dampening of the response to familiar (i.e., standard) stimuli.

Importantly, if with further research the pattern of deficits in VMMN in AD compared to those in normal ageing were found to be robust, then VMMN may prove to be an important peripheral marker of the changes in brain function associated with the presence of AD[154]. The fact that the current AD related anomalies in automatic processing were illustrated with a group consisting of only 8 individuals was encouraging in terms of the diagnostic application of VMMN.

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[153] It is thought that these adaptive filter neurons may also help in the identification of novel objects in the environment. The enhanced activation of these cells to novel stimuli will presumably give those cells receiving their outputs, an advantage in any neural competition; shifting the attentional focus to any new items in the scene. As the organism increases contact with the item, the memory will be strengthened, synaptic weights will adjust and the activation of the adaptive filter cells will decrease, reducing the drive on attentional systems in turn. This will free the system to shift attention to the new item (Desimone et al., 1995).

[154] Further research must also be performed to determine the robustness of the greater detrimental effect on VMMN in AD in the right compared to the left visual hemisphere; such an effect may also be an important peripheral marker for the presence of AD.

CHAPTER FOUR: VISUAL SEARCH

4.1 THE VISUAL SEARCH TECHNIQUE

Visual search is a psychophysical technique that has been widely employed in the measurement of both automatic and attention-mediated visual processing.

Individuals are shown a visual display consisting of various numbers of irrelevant or distractor stimuli (independent variable) with or without a pre-specified target stimulus. They are required to respond as quickly and as accurately as possible to the presence or absence of the target (whose position is uncertain in target present conditions). The time taken to detect the presence or the absence of the target (dependent variable) is recorded as the reaction time. The number of distractor items to be searched amongst in the display is varied from trial to trial with the display remaining visible for a pre-specified time limit.

The results of visual search (i.e., how efficiently the target or its absence is detected) depend upon the properties of the targets and the distractors. With some combinations, the number of distractors in a display has little effect on the time taken to detect the target or its absence; in others, an increase in the number of distractors results in an increase in the amount of time required to detect the target or its absence.

If target detection is associated with a small increase in reaction time as the number of distractors increases or if indeed target detection is virtually unaffected by the number of distractors, then target detection is said to have occurred by 'pop-out'. In pop-out the target appears to leap from the display without any effort on the part of the individual. Target detection which shows a more pronounced increase in reaction time with an increase in the number of distractors is said to have been achieved by 'serial' search.

The most common way of characterising visual search task performance has been to display the results in terms of the slope of the response time (RT) as a function of the total number of items in the display. The RT/(number of items) slope value has generally been interpreted as representing the time per item associated with stimulus comparison and therefore as an index of the attentional demand of the visual search. According to Treisman and colleagues, searches that produced slope values of up to 10 msec/item were indicative of automatic[155] (i.e., pop-out) visual processing. Slope values above 10 msec/item represented a large increase in the time taken to detect the target as the number of distractors increased and were therefore indicative of serial search[156] [157]. Serial search was described as being the

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[155] (i.e., search for a target that could be performed without the need for visuospatial attention).
[156] Slope values at or below 10 ms/item are generally taken as a bench mark for parallel, i.e., pop-out search because it is generally acknowledged that it is implausible that serial processing can be

result of the need for the serial application of visuospatial attention across the visual field, with the focusing of attention on each item in turn[158].

The automatic visual processing that results in pop-out has generally been considered to be a property of the striate cortex. By comparison, the attention-related visual processing characterised by serial search has been associated with the parietal cortex.

As neuropathological evidence has revealed a relative sparing of the striate cortex in AD compared to normal ageing one would expect therefore that the functional integrity of the striate cortex would also be spared. If this is indeed the case then one would predict that automatic visual search (i.e. pop-out), which is thought to occur in the striate region, would be relatively spared in AD in relation to normal ageing. The high pathological load in the parietal cortex in AD compared to normal ageing would suggest however that serial search (thought to be mediated by the parietal region) would be less efficient in AD compared to normal ageing.

The aim of the present study was therefore to use pop-out and serial visual search in an attempt to determine how automatic and attention-related visual processing were affected in AD compared to normal ageing. A further objective was to ascertain whether the results of such tests could have the potential for use as peripheral indicators of the presence of AD.

The following sections provide a description of the theoretical and practical aspects of visual search. A review of previous studies which have used this technique to determine the effects of ageing, AD and other neurological disorders on visual processing will also be presented.

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physiologically realised at a rate that would produce flat search functions (Crick, 1984; Gilchrist, Humphreys and Neumann and Riddoch, 1997).

[157] In addition to measuring the time taken to detect the presence of a target, the time taken to detect the absence of a target is also measured (this is to ensure that participants are actually responding to the target and not just responding randomly, i.e., whether or not they have actually detected the target). In serial search tasks the ratio of the slope values for target absent trials to target present trials was often quoted as nearly 2:1. Such a result was interpreted by Treisman and colleagues as indicating a serial self-terminating search strategy, again indicative of the serial focusing of attention on each item in turn. This was because to find a target that is present and randomly located requires searching on average half of the items in the array, but to determine that no target is present requires searching all of the items. So search was seen as exhaustive on target absent trials because certainty of absence requires investigation of all items and self terminating on detecting the target on target present trials (Treisman and Gelade, 1980).

[158] Although it is now clear that pop-out and serial search do not represent a strict dichotomy between automatic and attention-mediated visual processing (Wolfe, 1994), by using appropriate stimuli they are still used extensively to illustrate such processing.

4.2 THEORETICAL ASPECTS OF VISUAL SEARCH

(A) FEATURE INTEGRATION THEORY

One of the first and most influential explanations of why some distractor-target configurations resulted in pop-out while others did not, was that advanced by Treisman and colleagues (e.g. Treisman, 1982, 1988; Treisman and Gelade, 1980 and Treisman and Sato, 1990) in their theory of visual processing known as feature integration theory (FIT).

The ideas put forward in this theory were extensions of Neisser's (1967) concept that two levels of processing were needed to synthesise perceptual objects. The simple features of which objects are formed are identified first, followed by the determination of its shape and meaning from the relative positions of these simple features[159].

According to FIT an initial stage of visual processing registered or extracted simple features such as colour, orientation, spatial frequency, brightness and direction of movement that were present within the visual scene. The mechanism by which such features were extracted was described in terms of the activation produced in sets of spatiotopically-organized 'maps' of the visual field, each automatically encoding and signalling the presence of a particular feature in parallel across every location in the visual field[160].

Treisman and colleagues suggested that the search for a target defined by a single feature could be performed rapidly (i.e., could pop-out) because its presence resulted only in the activation of the relevant feature map[161]. Such activation enabled the feature to automatically draw attention to itself thus resulting in its rapid identification as the target. Because attention does not have to be deployed over every distractor to determine whether it is a target or not, the time taken for pop-out search is independent of the number of distractors present in the visual field. According to Treisman and colleagues, a green horizontal target surrounded by red horizontal distractors can be detected by pop-out because the target can be differentiated from the distractors on the basis of a single feature, i.e., colour. However, a target consisting of a red vertical bar in a field of green vertical bars and red horizontal bars would not pop-out because it was surrounded by distractors which shared both of its features, i.e. both colour and orientation[162]. According to FIT, the identification of a target defined by a conjunction of features

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[159] Known as the 'shape from relative position mechanism, Neisser, (1967)

[160] It was assumed that the dimensions of a stimulus were processed along functionally independent pathways and that information conveyed by these pathways should provide the basis for the feature maps.

[161] (i.e., although 'horizontal' is signalled for both target and distractors, 'green' is only signalled by the target, therefore making the target unique amongst the distractors).

[162] (i.e., the target has no 'unique identifying feature).

required focused attention[163] which had to be moved serially (i.e. deployed around the visual field from item to item) until the target was found.

Consequently search for a target described by a conjunction of features was seen as producing an increase in search time as the number of distractors increased. The greater the number of distractors, the longer it would take for attention to be moved around and applied to each of them in turn, i.e., the longer it would take to determine that each distractor was not the target. Such a search was known as serial search[164].

However, as studies of visual search progressed the re-interpretation of some aspects of the FIT became necessary and the idea of a distinct boundary between serial and pop-out visual search based on slope values was modified.

(B) RECENT FINDINGS IN VISUAL SEARCH STUDIES

More recent research, with a considerable variety of different distractor-target configurations has revealed that visual search slope functions form a continuum of values rather than a strict dichotomy. Such a range of values indicated that visual search tasks could be interpreted in terms of requiring different amounts of attention. Those with very low slope values being automatic or requiring very little attention and those with larger values requiring larger amounts of attention-related processing.

It also became established that some higher-level visual processing could (depending upon the target /distractor configuration) also be processed automatically. For example, targets with certain conjunctions of features were found to be detected by pop-out. Examples of such processing included targets defined by 'depth from shading' (Ramachandran, 1988; Kleffner and Ramachandran, 1992); 'three dimensional structure' (Enns and Rensink, 1991; Aks and Enns, 1992); 'depth and colour' and 'depth and motion' (Nakayama and Silverman, 1986; see Trick and Enns (1997). (See Heathcote and Mewhort, 1993 for a review of these studies).

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[163] According to FIT, targets made up of conjunctions of features represented 'high-level' stimuli and therefore required attention for identification.

[164] The results from such studies were taken as indicating that only very simple stimulus attributes could be processed automatically, a suggestion that was also propounded by Johnston and Dark (1986). Johnston and Dark suggested that stimulus processing outside the attentional spotlight was restricted mainly to simple physical features, with higher level processing requiring that spatial attention be directed to the stimulus.

Such results indicated therefore that targets made up of complex visual stimuli could be identified with much less need for the serial application of visuospatial attention, (i.e., with less attentional demand) than originally suggested by Treisman and colleagues in their feature integration theory.

(C) FACTORS DETERMINING THE TYPE OF VISUAL SEARCH THAT OCCURS

Several factors have now been found which determine how efficiently a target can be detected. Whether a target is detected automatically (i.e., by pop-out) has been found to be a function of several parameters of both the target and its surrounding distractors. Duncan and Humphreys (1989) and Nothdurft (1991, 1993) for example, showed how the featural similarity among distractors and the similarity of targets and distractors could have a profound effect upon visual search performance. Search becomes more efficient, i.e., relies less upon attentional processing, as a function of decreasing similarity between the target and distractors. Search efficiency is also increased by increasing similarity among the distractors[165].

In a review of numerous visual search studies, O'Toole and Walker (1997) and Wolfe (1994) determined that as a rule of thumb, pop-out tends to occur for features with large target-distractor differences, with search becoming less efficient (i.e., more serial) as target-distractor similarity increases and as distractor inhomogeneity increases. In addition, Wang, Cavanagh and Green (1994) found that familiarity[166] could also result in pop-out in visual search, but only when the target was unfamiliar and the distractors were familiar[167].

(D) GUIDED SEARCH

To accommodate the more recent findings of visual search studies a theoretical interpretation of the results known as 'guided search' (an update of FIT) was proposed (Wolfe, Cave and Franzel, 1989; Cave and Wolfe, 1990; Wolfe, 1992; Wolfe, 1994; see also Treisman and Sato, 1990).

According to guided search, the information gathered by the initial, parallel stage of processing (i.e. feature extraction) is in some cases able to restrict or guide, the deployment of attention to those parts of

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[165] Duncan and Humphreys (1989) proposed that homogenous distractors can group together and thus separate from the target enabling efficient search, whereas heterogeneous distractors fail to group together and group instead with the target, resulting in inefficient search for the target. Duncan and Humphreys suggested that the reason that the search for single feature targets was faster than the search for conjunction targets was because the distance in the similarity between the target and the distractors was larger in the single feature task than in conjunction tasks.

[166] A property of memory and not stimulus per se.

[167] It was suggested by Wang et al, (1994) that familiarity might facilitate the grouping of background items which then facilitates the pop-out of the target. Wang et al., suggested therefore that the

the visual field most likely to contain the target. Guiding attention to the most likely location of the target means that attention does not have to be serially deployed over the whole of the visual field until the target is found. Guided search, the result of the interaction of parallel and serial mechanisms, therefore increases the efficiency of attention-related visual processing. According to Wolfe (1994) the extent to which attention could be guided to the target explained the existence of various degrees of serial search.

Wolfe (1994) also highlighted the importance of considering both bottom-up and top-down processing in visual search. Bottom-up or stimulus driven processing was seen as a function of the dissimilarity between the target and distractors. According to Wolfe, a target which was very different to the distractors was seen as causing high 'activations' at the target's location in each feature map[168]. The comparison of the activity in the feature maps resulted in the identification of the location with the highest activation and this would be the location to which attention was directed. The processes under attentional control subsequently determine the identity of the item[169]. Items are examined in a serial self-terminating manner, beginning with the most active item and continuing in order of decreasing activation until either the target is found or no items remain.

According to Wolfe (1994) pop-out was the result of bottom-up processing and occurred when the properties of the target were able to produce the highest level of activation regardless of the number of other items, thus causing attention to be immediately attracted to its location. In search for targets defined by certain kinds of feature conjunctions bottom-up processing is not sufficient to distinguish between the target's location and the locations of the distractors. This is because when the target and distractors share features, for example orientation and size, both the orientation and size map are activated in each location in which either a target or distractor is present.

However, top-down knowledge of the identity of the relevant features of the target leads to an increase in the activation of the specific features of which the conjunctive target is composed. As a result, the conjunctive target has a tendency to be more strongly activated and consequently can efficiently guide the attention to its location. This results in a reduction in the need to serially apply attention throughout the visual field and results therefore in faster target detection[170]. If the target-distractor

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familiarity of each item must be available very rapidly and that the test stimuli must make contact with memory before the parallel search process terminates.

[168] Guided search assumes that the activation levels of each feature map are summed to form an activation map and that attention is directed to the location with the highest level of activation.

[169] According to Wolfe (1994) for the purposes of guiding attention, activation at a locus does not contain any information about its source, i.e., high activation from the colour map looks the same as high activation from the orientation map, with the purpose of the activation map being to direct attention. In the absence of endogenous commands to the contrary, attention will be placed at the locus of highest activation. The processes under attentional control then make the decision about the actual identity of the item.

[170] (not as quick as pop-out but quicker than just the random deployment of attention around the visual field).

configuration is such that guidance cannot take place then search for the target will take longer as it necessitates deployment of attention over all distractors.

The guided search model suggests therefore that visual search can be performed either by predominantly bottom-up processes, resulting in pop-out, or the combination of bottom-up and top-down processes tending to result in a more serial type of search.

4.3 THE AREAS OF THE BRAIN INVOLVED IN POP-OUT AND VISUAL SEARCH

Although the neurophysiological basis of pop-out is not yet clear, this automatic visual processing has long been considered a property mainly of the striate cortex (Treisman, 1988). Several studies have revealed that neurons in the striate cortex have physiological (single unit) response correlates of perceptual pop-out. For example, Kastner et al. (1997) found that in the macaque monkey, a considerable number of neurons responded preferentially for orientation contrast stimuli[171] rather than for fields of elements of similar orientation. According to Kastner et al. (1997) as monkeys show texture segmentation and pop-out effects similar to that in humans, such neurons may therefore form the neural basis for pop-out. Sensitivity to feature contrast has also been found for other dimensions such as colour, luminance and stereo disparity (Nothdurft, 1991, 1993, 1995).

Visual search that cannot be performed automatically and requires instead the application of visuospatial attention has by contrast, been described as being dependent upon higher level visual processing areas, particularly the parietal cortex (Treisman, 1988). The involvement of the parietal lobes in attention-mediated visual processing and in shifting visuospatial attention between locations throughout the visual field is well established (see Corbetta et al., 1993 and Posner and Dehaene, 1994 for a review). The involvement of the parietal lobe in serial but not pop-out visual processing has been investigated by Corbetta et al., (1995). They used PET to determine whether the parietal lobe was active when participants searched for targets defined by a single colour or motion feature (i.e., those able to be processed by pop-out) or for targets defined by the conjunction of colour and motion (i.e., those requiring the application of visuospatial attention for detection). Significant activity was found in the parietal lobe (in particular the superior parietal lobule) only for the conjunction task.

Lesions of the parietal lobes have also been shown to slow the shifting of visuospatial attention in serial visual search tasks, while leaving performance on pop-out tasks unaffected (Arguin, Joanette and Cavanagh, 1993 and Parasuraman et al., 1992).

The dependence of pop-out and serial visual search on the functional integrity of different areas of the brain has led to their use in assessing patterns of visual impairment in numerous clinical populations,

such as head injury (Heinze, Munte, Gobiet, Nieemann and Ruff, 1992) and Parkinson's disease (Troscianko and Calvert, 1993).

The effects of AD on such processing in relation to that found in normal ageing have however received very little investigation. The focus of the present study was therefore to characterise the changes in both pop-out and serial processing that may occur with normal ageing and AD.

4.4 VISUAL SEARCH AND AGEING: PREVIOUS RESEARCH.

Evidence from neuropathological and neuroimaging studies[172] indicates that the striate cortex is relatively spared from the deleterious affects of ageing compared to the parietal cortex. One would expect therefore that ageing would be accompanied by greater deficits in attention-related compared to automatic visual processing. One would also expect therefore to see a greater decrement in serial compared to pop-out search with normal ageing. Although studies have looked at the effects of normal ageing on such visual processing, they have been few in number.

Plude and Doussard-Roosevelt (1989) compared the performance of young and older adults on pop-out and serial conjunction search and found that whereas pop-out search was minimally affected by ageing[173] the efficiency of serial search was significantly reduced compared to that in younger adults[174]. Oken, Kishiyama and Kaye (1994) also found that serial search was more affected by ageing compared to pop-out[175]. Similar results were also found in studies by Folk and Lincourt (1996); Zacks and Zacks (1993) and Madden, Pierce and Allen (1996)[176].

Folk and Lincourt (1996) suggested that a decline in the ability to use the top-down guidance of spatial attention to improve search efficiency[177] may be the cause of the observed age-related differences in slope values in serial search performance[178]. In addition, Greenwood et al. (1997) found that older adults

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[171] (i.e., a stimulus of a different orientation to the surrounding items).
[172] As described in chapters one and two of the present thesis.
[173] Older adults produced near zero slopes (for both target present and target absent conditions) as did the younger adults. As there was no statistically significant difference in the performance between the two groups Plude and Doussard-Roosevelt concluded that such automatic visual processing was relatively age-insensitive.
[174] Older adults exhibited larger slope values for both target present and target absent conditions compared to those for younger adults.
[175] There was no significant difference in pop-out performance between young and older adults, there was however a significant difference between the young and older for the serial task.
[176] The age difference in search rate was constant over central versus peripheral target location, indicating that this age difference was not determined entirely by an age-related reduction in the useful field of view.

[177] See Wolfe's (1994) 'guided search' model.
[178] Folk and Lincourt's (1996) results also indicated that although generalised cognitive slowing may indeed play a role, it does not provide a complete account of the age effects observed; the age effects remained after a general slowing transformation was applied to the young data. This suggested therefore

had difficulty in controlling the spatial focus of attention in serial search tasks. The results of these studies did therefore support the general idea of a greater decrement in serial compared to pop-out search in normal ageing.

That some of the effects of normal ageing could be revealed by visual search led to the use of this technique in the determination of the patterns of change in visual processing associated with neurological disorders. Some of the first studies to determine whether abnormalities in visual search task performance could be indicative of pathological change were those performed by Troscianko and colleagues who measured the effects of Parkinson's disease on target detection.

4.5 VISUAL SEARCH AND PARKINSON'S DISEASE

A study performed by Troscianko and Calvert (1993) revealed that compared to healthy older adults individuals with Parkinson's disease[179] (PD) were unable to elicit normal visual pop-out. Instead their performance, although having a parallel component, was partly serial in nature[180]. Later work by Weinstein, Troscianko and Calvert, (1997) studied both parallel and serial visual search in PD. In addition to replicating the results of their earlier study (Troscianko and Calvert, 1993), they found evidence for the normal processing of serial search in PD. Such results implied that the automatic visual processing associated with the normal elicitation of pop-out was detrimentally affected in PD whereas the attention -related, higher level visual processing associated with serial visual search was relatively preserved.

Troscianko and Calvert (1993) concluded that in PD, the inability to process information automatically would be expected to place a heavy load on serial mechanisms. However, if this were the case then one would expect individuals with PD to exhibit less efficient serial visual search due to the extra load placed upon it; or perhaps a reduction in the efficiency of search guidance due to an abnormally functioning parallel processing stage (see Wolfe, 1994). However, Weinstein's et als' (1997) results indicated that serial search was not detrimentally affected in PD.

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that the observed age-related decline in serial search reflected a task-specific deficit rather than just a general slowing of cognitive processes.

[179] Parkinson's disease is a progressive neurodegenerative disorder, with the peak age of onset in the sixth decade. Classic signs and symptoms include tremor, rigidity, akinesia and disturbances of posture (see Adams and Victor, 1993 and Lezak, 1995 for reviews). As a result of progressive basal ganglia dysfunction, causing the degeneration of the substantia nigra, the neurotransmitter dopamine is greatly depleted in Parkinson's disease. The motor symptoms of PD however emerge only after dopamine levels in the brain are very substantially reduced.

[180] Control experiments indicated that this failure of pop-out was not due to slow response times, an inability to detect the target or to crowding effects.

Troscianko and Calvert (1993) interpreted the abnormal pop-out in PD in terms of dopamine-related abnormalities in early visual processing particularly those affecting V1 (the striate cortex). Evidence from other types of investigation has also supported the idea of a PD-related abnormality in early visual processing. Abnormalities in visual evoked potentials (Bodis-Wollner et al., 1982, 1987; Bodis-Wollner, 1988); abnormalities in sensitivity to spatial contrast (Harris et al., 1993; Regan and Neima, 1984; Bodis-Wollner et al, 1987) and abnormalities in orientation processing (Calvert et al, 1990, 1992) have all been found in PD.

However more recent evidence from neuroimaging studies suggests that PD is characterised by functional decrements in the striate, extrastriate and parietal cortex (Eberling et al., 1994). The observation of striate cortex deficits provided support for Troscianko and Calvert's suggestion that functions associated with this area are abnormal in PD. However, the finding of a functional deficit in the parietal cortex would suggest that one should also find some abnormality in serial search as well (but see Weinstein et al., 1997). It has become clear however that the effects of PD are not well demarcated or consistent (see for example Goto, et al.,1993)[181].

Although the interpretation of the visual search results in PD may be problematic, the specific deficit in automatic processing in PD compared to age-matched older adults did demonstrate the potential use of the visual search technique for characterising the presence of a neurological disorder.

4.6 VISUAL SEARCH AND ALZHEIMER'S DISEASE (AD)

Very few studies of visual search performance in AD have been performed. However the results of these studies show a distinct pattern. For example, Grewal (1989) showed that compared to older adults the increase in reaction time with increasing distractor display size was greater in magnitude for individuals with mild to moderate Alzheimer's disease. This indicated an AD-related deficit in attention-related serial visual search. Oken, Kishiyama and Kaye (1994) reported the results of a pilot study which, like the results of Grewal's (1989) study, revealed a greater decrement in performance on a serial search task for individuals with AD compared to older adults. Oken et al., (1994) also found that pop-out was relatively unaffected by AD compared to normal ageing. Greenwood, Parasuraman, and Alexander (1997) also found the pattern of preserved pop-out together with deficits in serial search even in individuals in the early stages of AD compared to healthy older adults. The decrements in serial search in AD have been attributed to an underlying deficiency in the processes involved in successively engaging and disengaging visuospatial attention from one item to the next. Deficiencies in engaging and

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[181] The finding of abnormal automatic processing but normal attention-related processing in PD also casts some doubt on the current interpretation of the functional organisation of the visual system. One has to ask the question of how apparently normal later stage visual processing is able to occur in the presence of an abnormal early stage.

disengaging visuospatial attention in AD have also been found by other measures of attentional function [182, 183].

The results from these studies correspond to the suggestion that: (1) because the striate cortex is relatively spared in AD, automatic visual processing, such as pop-out is relatively spared compared to normal ageing, (2) because the parietal cortex undergoes greater decrement in AD compared to normal ageing, attention-mediated visual processing, such as serial search is reduced in efficiency compared to normal ageing.

Importantly, visual search studies have revealed a difference in the pattern of visual deficits in PD and AD indicating therefore that such techniques may be able to reveal differences between neurological disorders.

4.7 EXPERIMENTAL SECTION

The aim of the present study was therefore to attempt to replicate the results from previous studies looking at the effects of ageing and AD on visual search performance and to explore the associated patterns of functional deficit in greater detail. In an attempt to determine the potential suitability of such tests for diagnostic purposes the participants were tested in a clinical, as opposed to a laboratory setting.

The predictions for the study were that:

1) In normal ageing there would be no decrement in automatic (pop-out) visual search.
2) In normal ageing there would be a greater decrement in serial visual search compared to that in younger adults.
3) In AD there would be no decrement in automatic (pop-out) visual search compared to normal ageing.
4) In AD there would be a greater decrement in serial search compared to normal ageing.

In addition to the measurement of automatic and attention-related components of the visual search tasks (measured in terms of the slope values of reaction time and distractor number), measures of intercept

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[182] The interpretation of reduced efficiency of serial search in AD is supported by the results of other methods of measuring visuospatial attention in AD; see Greenwood et al., 1997 for a review and reported in section 2.26 of chapter two of the present thesis.

[183] The impairment in shifting visuospatial attention could also be a contributing factor to the difficulties individuals with AD have in performing composite-object identification or cancellation tasks (Della Sala, Laicona, Spinnler and Ubezio, 1992) in which attention must be successively directed to different parts of a complex visual object or to different visual locations.

and % correct responses were also recorded to provide additional information regarding the effects of ageing and AD on the encoding and response components of visual processing.

4.8 STUDY ONE:

To determine differences between young adults, older adults and older adults with Alzheimer's disease in pop-out and serial visual search.

4.8(a) METHOD

PARTICIPANTS

The young adults were recruited from the postgraduate population of the University of Bristol, via poster appeal. The older adults were recruited from the 'research volunteer' data base at the BRACE Centre memory clinic and were known from previous cognitive and clinical screening investigations to have normal cognitive profiles and no known neurological deficit or significant medical disorder. Both young and older adults were free from neurologically associated medication and all had normal or corrected to normal vision[184]. The older adults and adults with AD had no clinically apparent cataracts or glaucoma and none were using eye drops[185]. All the participants were right handed and were not paid for taking part.

The individuals included in the AD group all had a recently determined diagnosis of probable AD according to NINCDS-ADRADA criteria and were free from any other neurological or psychiatric disorder and were not on any neurologically associated medication. The recruitment of this group was from the BRACE Centre memory clinic in Bristol.

In the AD group, the mean MMSE score was 20.6; for the older adult group the MMSE score was 28.8 (within the normal expected scores for older adults). None of the individuals with AD had presented with prominent visual symptoms and were assumed therefore not to have a 'visual' subtype[186] of AD. Verbal and written consent was obtained from all participants (and their carer in the case of individuals with AD).

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[184] This was checked by asking how their eyesight was, checking their available medical notes (in the case of individuals with AD) and asking all participants to identify the stimuli on the screen and to read out loud a set of written instructions. Several trials were performed and the results studied to ensure that they could perform the task.

[185] In the case of individuals with AD this was established by asking them and their partners/ carers and checking medical notes.

[186] See chapter one and two of the present thesis.

There were **5 young adults;** (2 male; 3 female), age range 27 to 34 years, (mean age 29.4 years); **5 older adults;** (3 male, 2 female), age range 66 to 81 years, (mean age 72.2 years) **and 5 adults with AD**; (1 male, 4 female), age range 65 to 82 years, (mean age 74.2 years)[187].

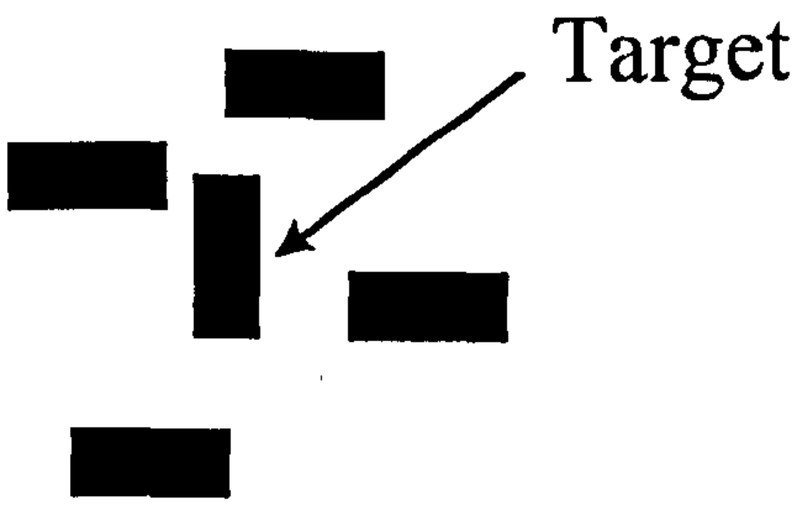
4.8(b) APPARATUS

All testing was performed in a room normally used for cognitive testing, with its normal level of ambient lighting. Only the participant and the experimenter were present.

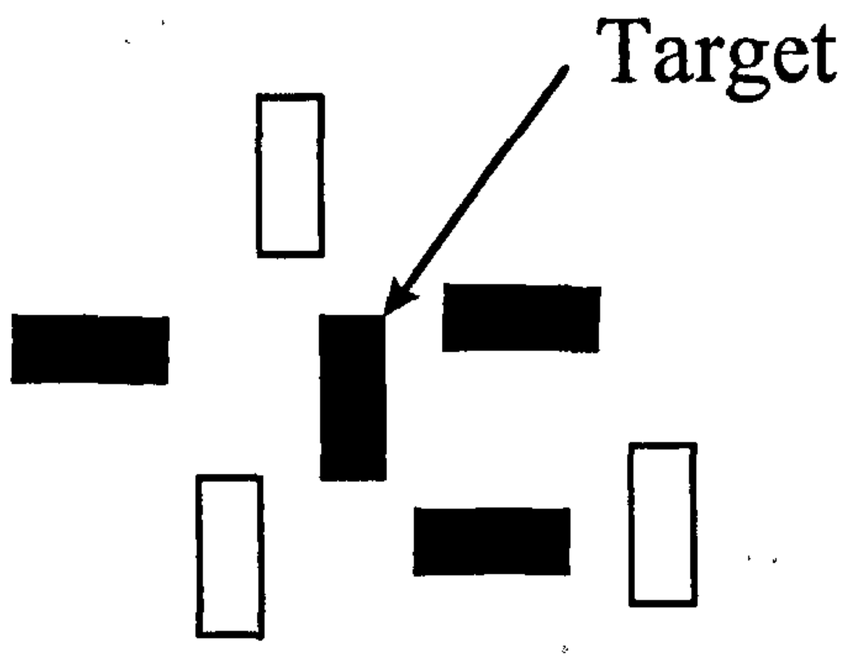
The stimuli were generated on an IBM PC system. The display was presented on a colour monitor on which just the green phosphor was activated. The area used to display stimuli subtended 17.3 x 10.6° at a viewing distance of 80 cm in front of the display monitor; the eye was at the same height as the centre of the monitor display. The luminance of the uniform green screen was 5.6 cd m^{-2}. The luminance of the dark bars was 4.3 cd m^{-2}. The luminance of the light bars in the conjunction experiment was 7.3 cd m^{-2} (giving a Michelson contrast of 13 % for both light and dark stimuli[188]). Each bar subtended 0.3 x 0.7 °. Each bar was located in a grid box but with a random internal pertubation and no bars touched each other. A stylised example of the type of display used in the experiments can be seen in figure 4.1.

FIGURE 4.1

(a) POP-OUT



(b) CONJUNCTION



[187] (The AD group originally consisted of 8 potential participants but one individual's diagnosis was altered just before the study commenced and two could not perform the task during the practice phase despite several attempts. No data was therefore recorded for these individuals).

[188] This value was used since a control experiment by Troscianko and Calvert (1993) suggested that the contrast response function was bottomed out at that value and therefore minor changes in perceived contrast would not be expected to affect the results, for young or older people. (Weinstein et al 1997).

Response to the presence or absence[189] of the target was indicated by the participant pressing one of two buttons mounted on a hand held box; pressing the red button if the target was present and the yellow button if the target was absent. The target present (red button) was always pressed by the right thumb and the target absent (yellow) button was always pressed by the left thumb. The buttons were large, easy to press and to hold. The target could appear at any location amid 3 possible arrays of items (16, 36, 81 target plus distractor arrays). If a button had not been pushed for more than 10 seconds the computer ignored that trial (but repeated it later); the whole area of the screen turned green and displayed an 'out of time' message. The run was restarted by pressing one of the buttons. Anticipatory responses of less than 100 msec were also rejected.

The order of stimulus presentation, i.e. target present or target absent, with 16, 36 or 81 items was randomly presented. There were 30 trials for each of the six conditions, i.e., 16, 36, 81 items with the target present and 16, 36, 81 items with the target absent. For the actual test no feedback was given about whether the response was correct or not. Reaction time to the detection of the target was recorded as was the percentage (%) of correct responses and stored on disc for subsequent off-line analysis[190].

For the pop-out task, participants were asked to respond to the presence or absence of a black vertical bar (target) amongst black horizontal distractors. For the conjunction task, participants were asked to respond to the presence or absence of a black vertical bar (target) amongst black horizontal and white vertical distractors. Response to the presence or absence of the targets was indicated by the participant pressing one of two buttons. (If a button had not been pushed for more than 10 seconds the computer ignored that trial; the screen displayed an 'out of time' message. The run was restarted by pressing one of the buttons. That trial was then repeated later.

4.8(c) PROCEDURE

Before data collection commenced participants were shown the apparatus and were given the opportunity to ask questions. After a description of the task requirements the participants were asked to perform a practice trial to ensure that they could understand the task, identify the target and the

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[189] Target absent responses were included to ensure that participants did not simply respond with a button press even though they had not detected the target.

[190] Due to the restricted time available to test visual search in individuals with AD it was not possible to determine the effects of crowding on target detection in the present study. However, the parameters of the present study were identical to those of Troscianko and Calvert (1993) who performed tests to ensure that the stimuli used did not to cause significant crowding effects in normal ageing (see Troscianko and Calvert, 1993).

distractors for each type of visual search task[191] and were able to use the buttons to respond appropriately. (Potential participants were excluded if they performed only at chance levels).The participants were told that there would be a target present on only 50% of the trials. The participants were then instructed to fixate on the fixation spot (which appeared at the centre of the screen 100 msec before the onset of each stimulus array) and when the stimuli appeared, to try and detect the target as quickly but as accurately as possible.

To reduce the likelihood of individuals (particularly those with AD) forgetting the task instructions several breaks were given throughout the procedure in which the task instructions were repeated. In addition, for the individuals with AD the test was also suspended and the instructions repeated if they repeatedly ran out of time as this may have been an indicator of them forgetting the task. Total testing time (i.e., to perform both tasks) ranged from 30 to 40 minutes. All participants performed the pop-out task first[192] and no feedback about performance was provided.

4.9 RESULTS

For each participant the mean reaction time (RT) and % correct responses were recorded for each item display (16, 36 and 81) for both target present and target absent trials of the pop-out and serial search tasks. Although particular emphasis was placed on the 'target present' data, the target absent data was also recorded and analysed to determine whether the search for an absence of a target could provide additional age or AD-specific measures.

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[191] The practice trials for the two visual search tasks were performed separately, each one performed just before the relevant trial, so as to avoid potential confusion.

[192] The pop-out task was always performed first because it was uncertain for each participant with AD, whether they would be able or want to, perform both tasks. So by measuring pop-out first ensured that a complete set of results would be obtained for one condition. Because the main aim of the present study was to characterise automatic visual processing in AD, pop-out was deemed the most important experimental condition.

4.9(i) REACTION TIME DATA

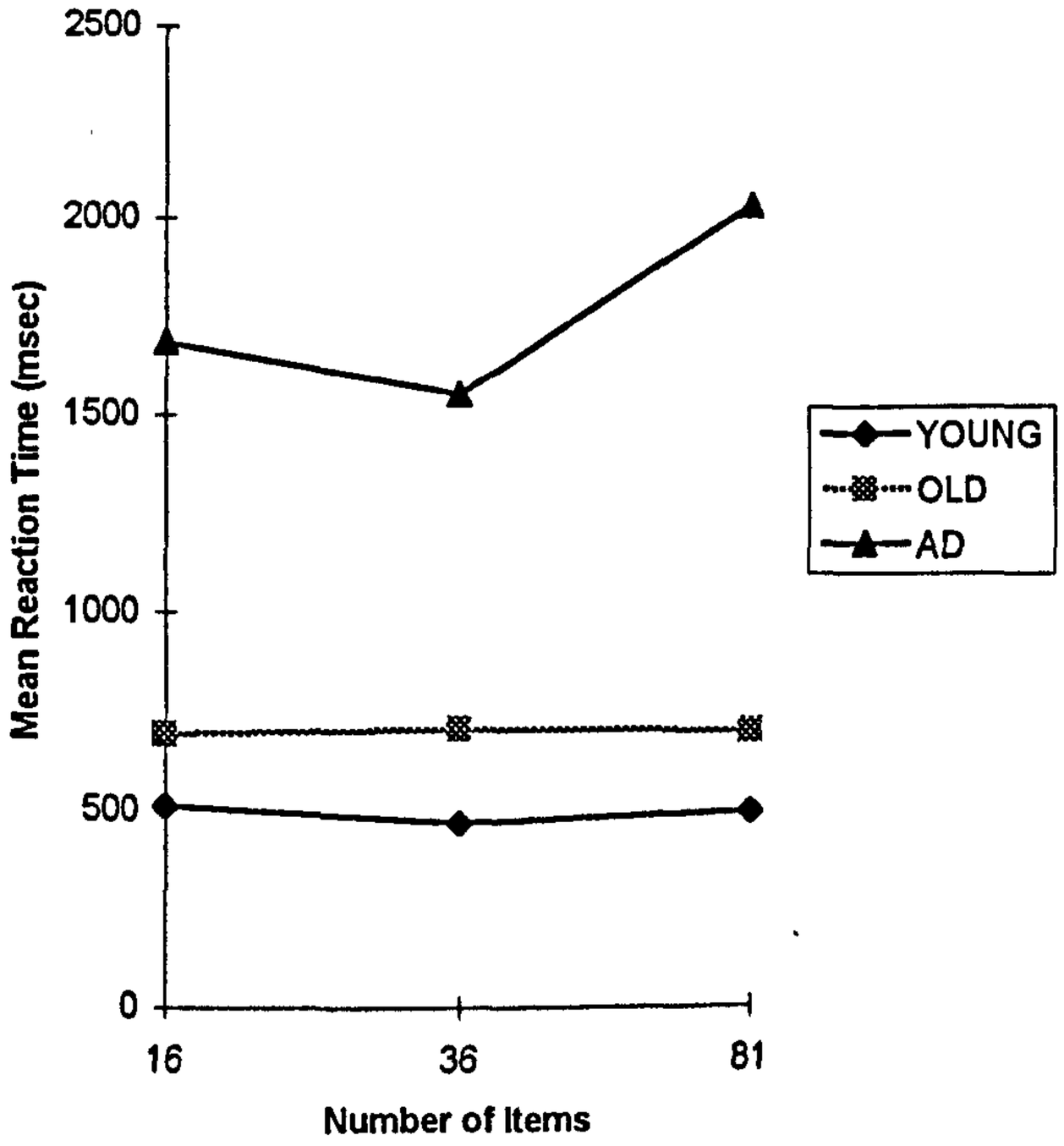
Table 4. 1 The mean reaction time for the Young, Older adults and AD groups, for the target present and target absent conditions of the 'pop-out' visual search task. (The raw data can be found in tables A4.1- A4.6 of the chapter four appendix).

YOUNG ADULTS		NUMBER OF ITEMS		
		16	36	81
TARGET PRESENT	REACTION TIME (msec)	511.9	468.1	498.7
	Standard deviation	65.9	41.1	56.7
TARGET ABSENT	REACTION TIME (msec)	666.2	698.2	777.8
	Standard Deviation	57	41.6	111.5
OLDER ADULTS				
TARGET PRESENT	REACTION TIME (msec)	692.2	707.1	701.3
	Standard deviation	85	89.5	89.6
TARGET ABSENT	REACTION TIME (msec)	1126.6	1287	1227.2
	Standard deviation	431.2	593.3	430.5
AD				
TARGET PRESENT	REACTION TIME	1683.5	1552.8	2030.3
	Standard deviation	1399.5	1246.6	1733.6
TARGET ABSENT	REACTION TIME (msec)	3483.6	3799.9	3732.5
	Standard deviation	2196.3	2406.9	2189.0

Table 4. 2 The mean reaction time for the Young, Older adult and AD groups, for the target present and target absent conditions of the serial visual search tasks. (The raw data can be found in tables 4.7-4.12 of the chapter four appendix).

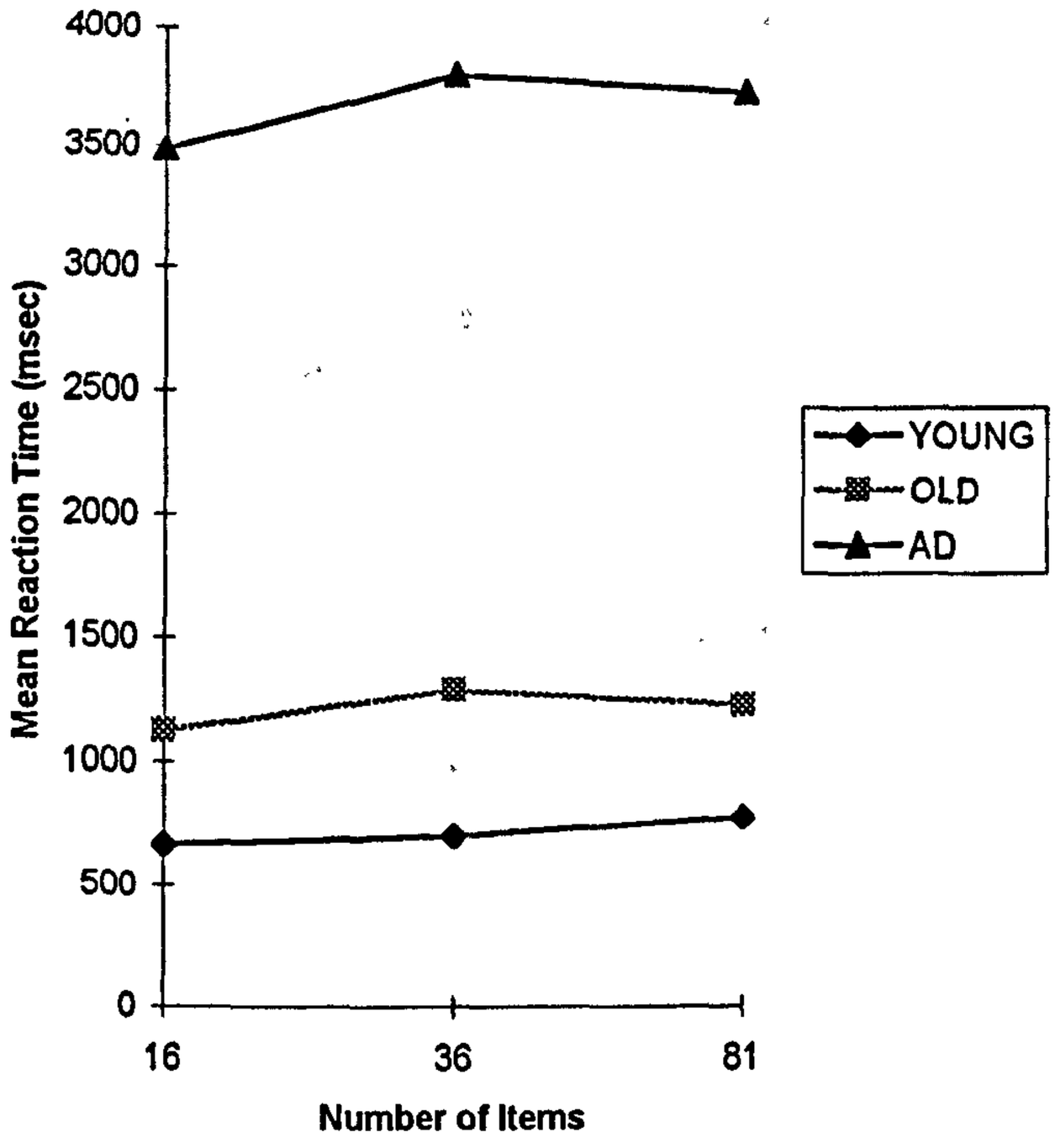
YOUNG ADULTS		NUMBER OF ITEMS		
		16	36	81
TARGET PRESENT	REACTION TIME (msec)	663.1	725.9	817.6
	Standard deviation	133.2	90.1	120.3
TARGET ABSENT	REACTION TIME (msec)	872.9	1348	1687.1
	Standard deviation	75.4	149.1	194.5
OLDER ADULTS				
TARGET PRESENT	REACTION TIME (msec)	934.3	1053.6	1233.6
	Standard deviation	171.1	126	294.3
TARGET ABSENT	REACTION TIME (msec)	1500.2	1908.5	2436.2
	Standard deviation	382.8	496.1	800.3
AD				
TARGET PRESENT	REACTION TIME	1982.2	2383.4	3480.7
	Standard deviation	844.7	1479.9	1515.3
TARGET ABSENT	REACTION TIME (msec)	3748.9	4293.1	4740.9
	Standard deviation	2321.7	2080.6	1955.7

Graph 4.1 The mean reaction time (msec) for each item number for the young adult, older and AD groups, for the target present condition of the pop-out task.



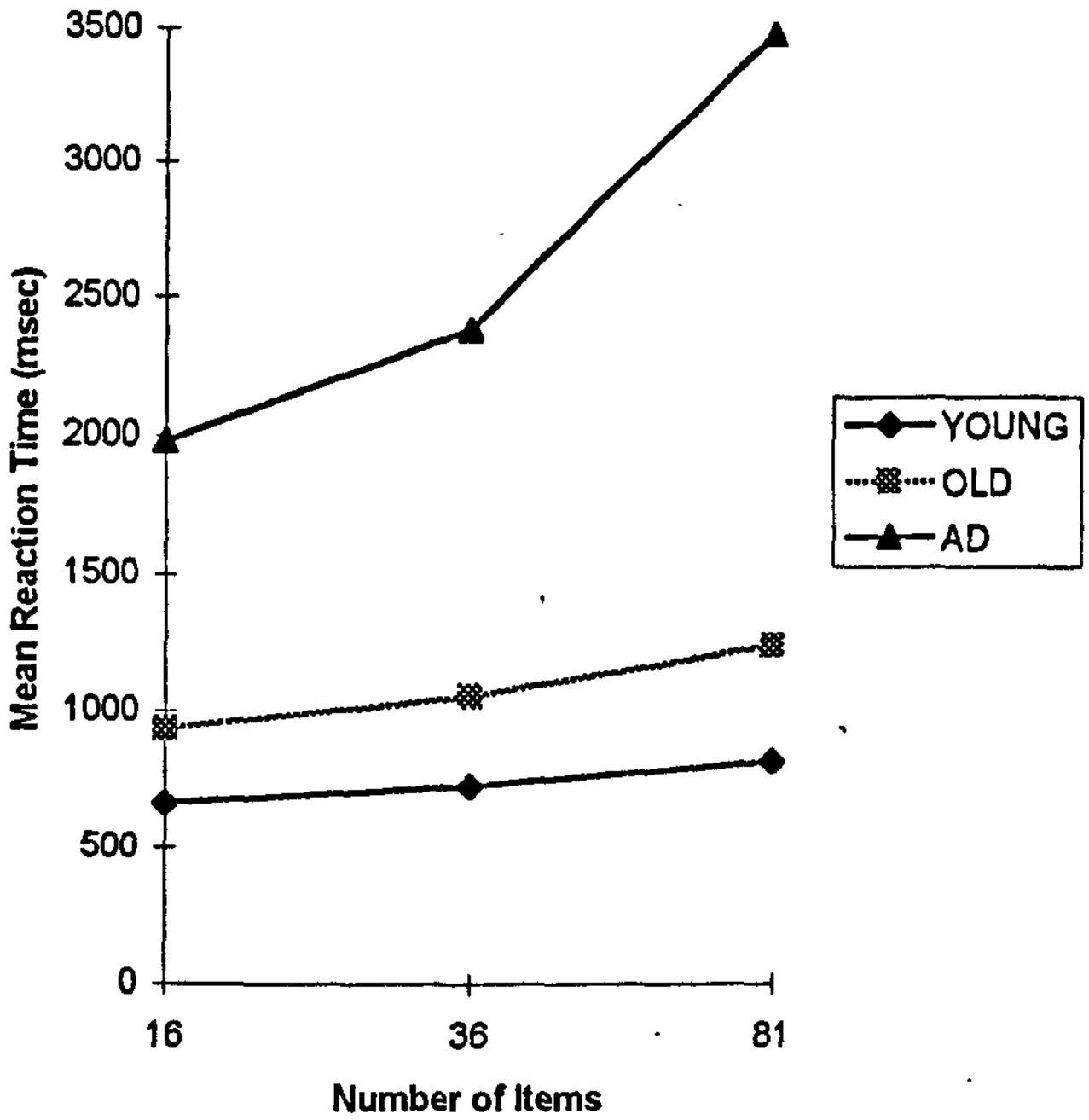
For all three groups the increase in the number of distractors was not accompanied by an overall linear increase in the mean time taken to detect the presence of the target. However, the pattern of reaction time values was different in AD compared to normal ageing. The mean reaction time was greater for the AD compared to the older adults over all item displays. Like the older adults, the AD group displayed a reduction in mean reaction time when the number of items increased from 16 to 36, but this reduction was greater in the AD group. Also for the AD group there was a greater increase in mean reaction time from 36 to 81 distractors than seen for the older adult group. Such differences would suggest therefore that individuals with AD are not as efficient at target detection when the target is surrounded by a large number, i.e., 81 items.

Graph 4.2 The mean reaction time (msec) for each item number for the young, older and AD groups, for the target absent condition of the pop-out task.



Compared to the target present condition, the AD group did not exhibit a sudden increase in RT for the 81-distractor condition. Over all three distractor conditions the mean time taken to detect and respond to the absence of the target was greater for the older adult compared to the younger adult group. For the AD group there was a further increase in reaction time compared to that of the older adult group.

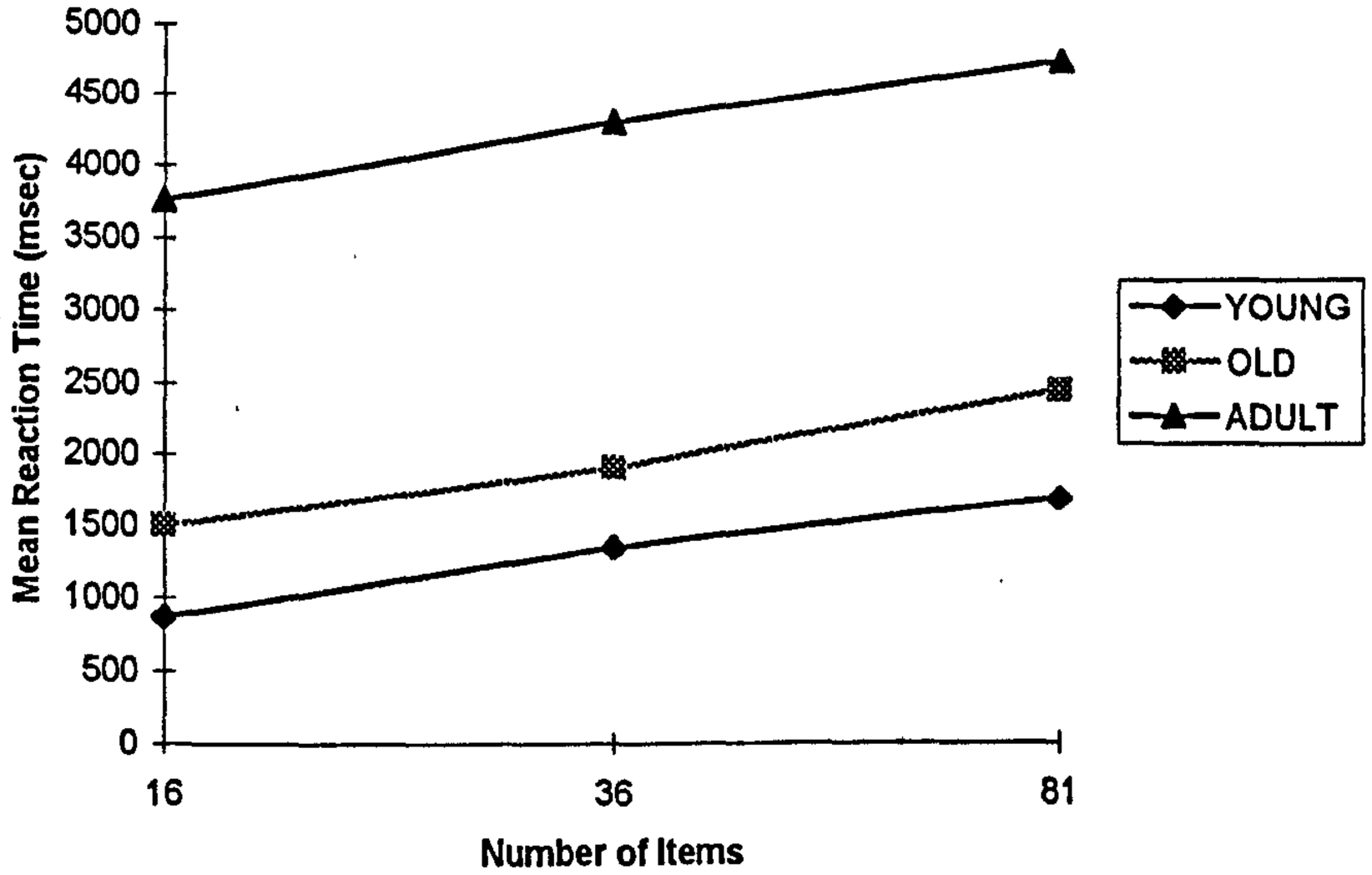
Graph 4.3 The mean reaction time (msec) for each item number for the young, older and AD groups, for the target present condition of the serial task.



The increase in the number of distractors resulted in a corresponding linear increase in the time taken to detect the presence of the target for all three groups. For both the young and older adult groups there was a gradual increase in reaction time as the number of distractors increased; for the AD group however the increase in distractor number from 36 to 81 was accompanied by a greater increase in reaction time than that indicated for the increase in distractor number between 16 and 36 distractors. This once again indicated that in AD target detection becomes less efficient at high numbers of items compared to normal ageing.

Over all three distractor conditions the mean time taken to detect and respond to the presence of the target was greater for the older adult compared to the younger adult group. For the AD group there was a further increase in reaction time compared to that of the older adult group.

Graph 4.4 The mean reaction time (msec) for each item number for the young, older and AD groups, for the target absent condition of the serial task.



The increase in the number of distractors resulted in a corresponding linear increase in the time taken to detect the absence of the target for all three groups.

Over all three distractor conditions the mean time taken to detect and respond to the presence of the target was greater for the older adult compared to the younger adult group. For the AD group there was a further increase in reaction time compared to that of the older adult group.

4.9 (ii) REACTION TIME/ DISTRACTOR NUMBER SLOPE DATA

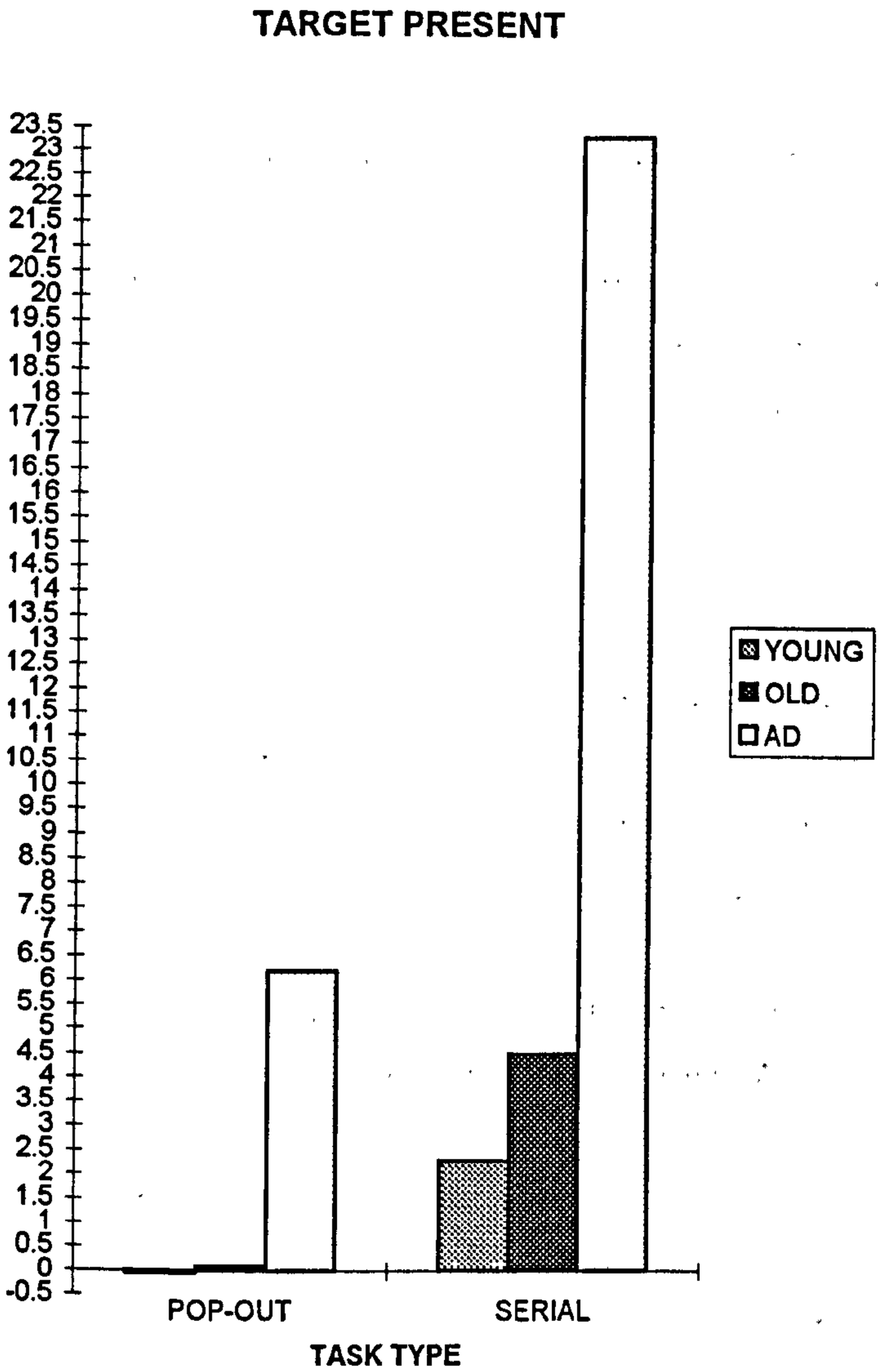
TARGET PRESENT DATA

Linear regression analysis of the mean time taken to detect the presence of the target amongst 16, 36 and 81 items was performed to obtain the mean slope and mean intercept value for each experimental condition to determine whether automatic (pop-out) or attention-related (serial) processing had occurred.

Table 4.3 The mean RT/ (number of items) slope values and standard deviation (sd) for the target present conditions for the young, older and AD groups for the pop-out and serial search tasks. (The raw data for these results can be found in tables A4.1-4.12 of the chapter four appendix).

	TARGET PRESENT SLOPE VALUES (msec/item)		
	YOUNG	OLD	AD
POP-OUT	-0.053 sd=0.37	0.094 sd=1.2	6.2 sd=6.8
SERIAL	2.3 sd=1.7	4.5 sd=3.9	23.3 sd=13.7

Graph 4. 5 The mean slope values (msec/item) for the target present condition of the pop-out and the serial visual search tasks, for the young, older and AD groups.



For the pop-out visual search task, all three groups detected the presence of the target in a pop-out manner; the mean slope values were all below 10 msec/item. The slope value for the AD group was however greater compared to that of the older group, indicating a reduction in the efficiency of pop-out in AD compared to normal ageing.

For the serial task, the mean slope values for the young and older adult groups were below 10 msec/item. This indicated that although the task had been designed to produce a serial type of search the young and older adult groups were able to detect the target by pop-out, i.e., automatically. The mean slope value for the AD group was however much greater than 10 msec/item and indicated that unlike the older adults, those with AD could not perform target detection on this task by pop-out, but had to resort to serial processing.

STATISTICAL ANALYSIS

A two-factor, one within and one between subjects ANOVA applied to the target present mean slope value data resulted in a significant main effect of group (young adults, older adults, AD), F (df 2,12), =6.992, $p < 0.01$; a significant main effect of search task (pop-out, serial), F (df 1,12) = 20.988, $p < 0.01$ and a significant interaction between group and task, F (df 2,12) = 7.009, $p < 0.01$.

Further analysis indicated that for the target present condition of the pop-out visual search task the difference in mean slope value between the young adult, older adult and AD groups failed to reach significance, F (df 2,20) = 1.23, $p > 0.05$. Such a result would appear to indicate therefore that pop-out is relatively spared not only in ageing but also in Alzheimer's disease.

Further analysis also indicated that for the target present condition of the serial search task the differences in mean slope value between the three groups reached significance, F (df 2,20) =12.756, $p < 0.0001$. The difference in mean slope value between the young and older adult groups however failed to reach significance t (df 8) =1.13, $p > 0.05$. Such a finding indicated that although serial search was somewhat reduced in efficiency in normal ageing it was not significantly so.

The difference in mean slope value between the older adult and the AD groups, did however reach significance t (df 8) = 2.6629, $p < 0.02$, with the AD group having the greatest decrement in processing. Such a result indicated therefore that AD resulted in a significantly greater impairment in serial search than that found in normal ageing. (There was a significant difference between both the young and AD groups, t (df 8) = 2.72, $p < 0.05$).

Although the conjunction task had been designed to produce a serial search function there was in fact no significant difference in mean slope value between the pop-out and serial search tasks, for the young

adults, F (df 1,12) =0.624, p> 0.05 or for the older adults, F (df 1,12) = 2.155, p> 0.05. Such a finding indicated therefore that the search for the target defined by a conjunction of features was performed very efficiently by both the young and older adults. This efficiency of processing did not however extend to the AD group as there was a significant difference in mean slope value between the pop-out and serial search tasks, F (df 1,12) = 32.226, p= < 0.0001, with the serial search task having the greatest value in the AD group.

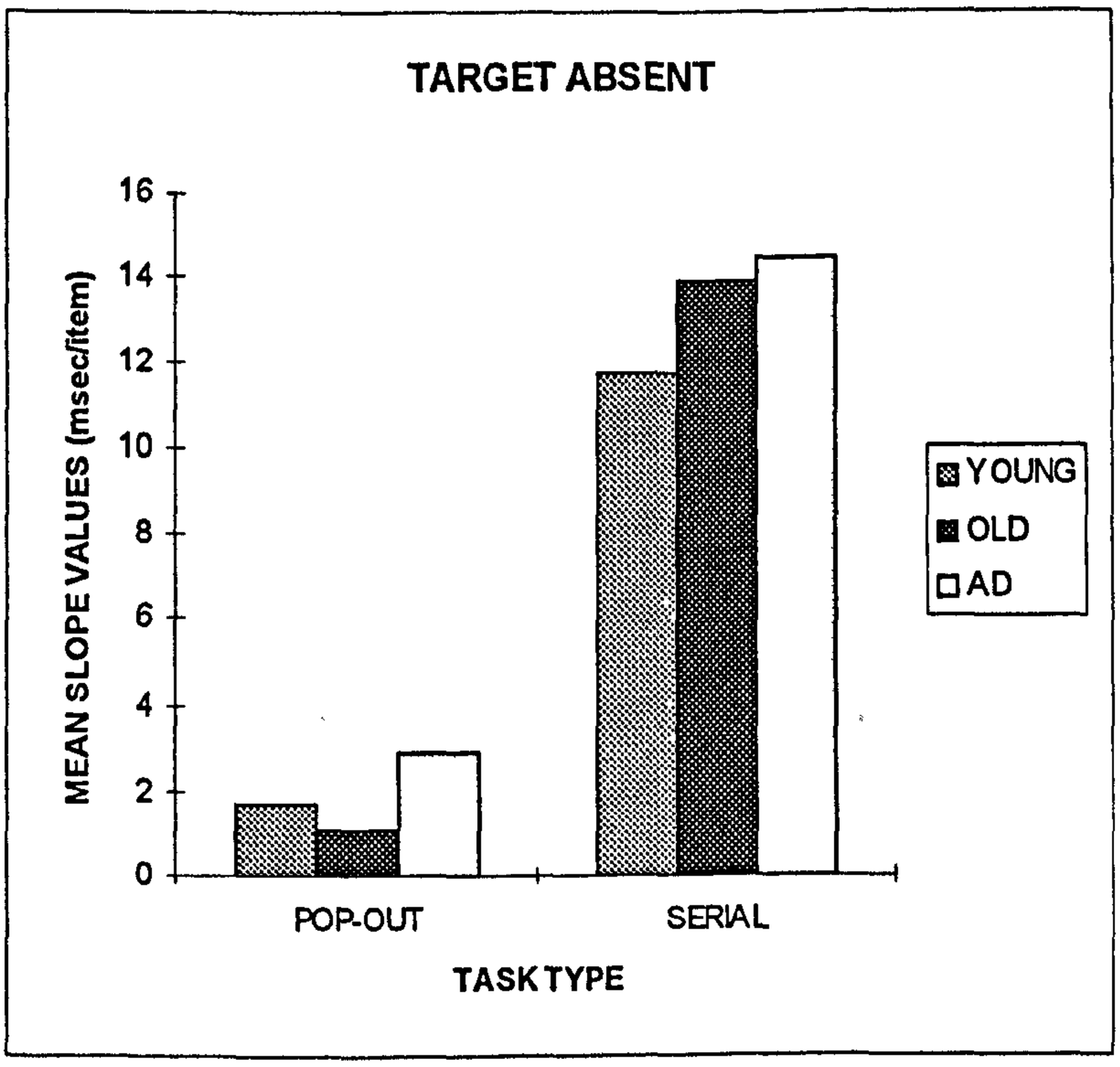
TARGET ABSENT DATA

Table 4.4 The mean RT/ number of items slope values and standard deviation (sd) for the target absent conditions for the young, older and AD groups for the pop-out and serial search tasks. (The raw data for these results can be found in tables A4.1-4.12 of the chapter four appendix).

	TARGET ABSENT SLOPE VALUES (msec/item)		
	YOUNG	OLD	AD
POP-OUT	1.7 sd=1.3	1.06 sd=1.1	2.93 sd=2.9
SERIAL	11.68 sd=2.2	13.9 sd=7.6	14.4 sd=14.5

GRAPH 4.6

The mean RT (msec) / item slope values for the target absent condition for the pop-out and serial visual search tasks for the young, older and AD groups.



For the pop-out task a greater slope value was obtained for the young compared to the older adult group and the slope value for the AD group was larger than that of the young group. For all three groups the slope values were greater for the serial compared to the pop-out task. For the serial task a greater slope value was obtained for the old compared to the young group and the slope for the AD group was larger than for the old group.

A two-factor, one within and one between subjects ANOVA applied to the target absent data for the mean slope value resulted in a significant main effect of task type F (df 1,12) 13.174, $p<0.01$, but no significant main effect of group, F (df 2,12) =0.217, $p> 0.05$ or interaction between group and task, F (df 2,12) = 0.072, $p> 0.05$.

Further analysis indicated that for the pop-out task, the greater decrement in young compared to older adults and the greater decrement in the AD compared to the old and young group failed to reach significance, F (df 2,20) = 0.076, $p>0.05$.

For the serial search task, the greater slope value for the old compared to the young and the greater slope value for the AD compared to the old group, failed to reach significance, F (df 2,20) =0.176, p>0.05.

In terms of slope value, for both the young adult group, F (df 1,12) =3.335, p >0.05 and the AD group, F (df 1,12) =4.397, p> 0.05, there was no significant difference between the pop out and serial tasks in terms of the mean slope value. For the older adult group however, there was a significant difference in slope value between the pop-out and serial tasks, F (df 1,12) =5.587, p<0.05, with the serial task having a greater value.

4.9 (iii) INTERCEPT DATA

In addition to determining the slope values for reaction time and item number, the mean intercept value was also obtained for each participant group, for the target present and target absent conditions for the pop-out and serial tasks. (The raw values for the intercept data can be found in tables A4.1-4.12 of the chapter four appendix).

TARGET PRESENT DATA

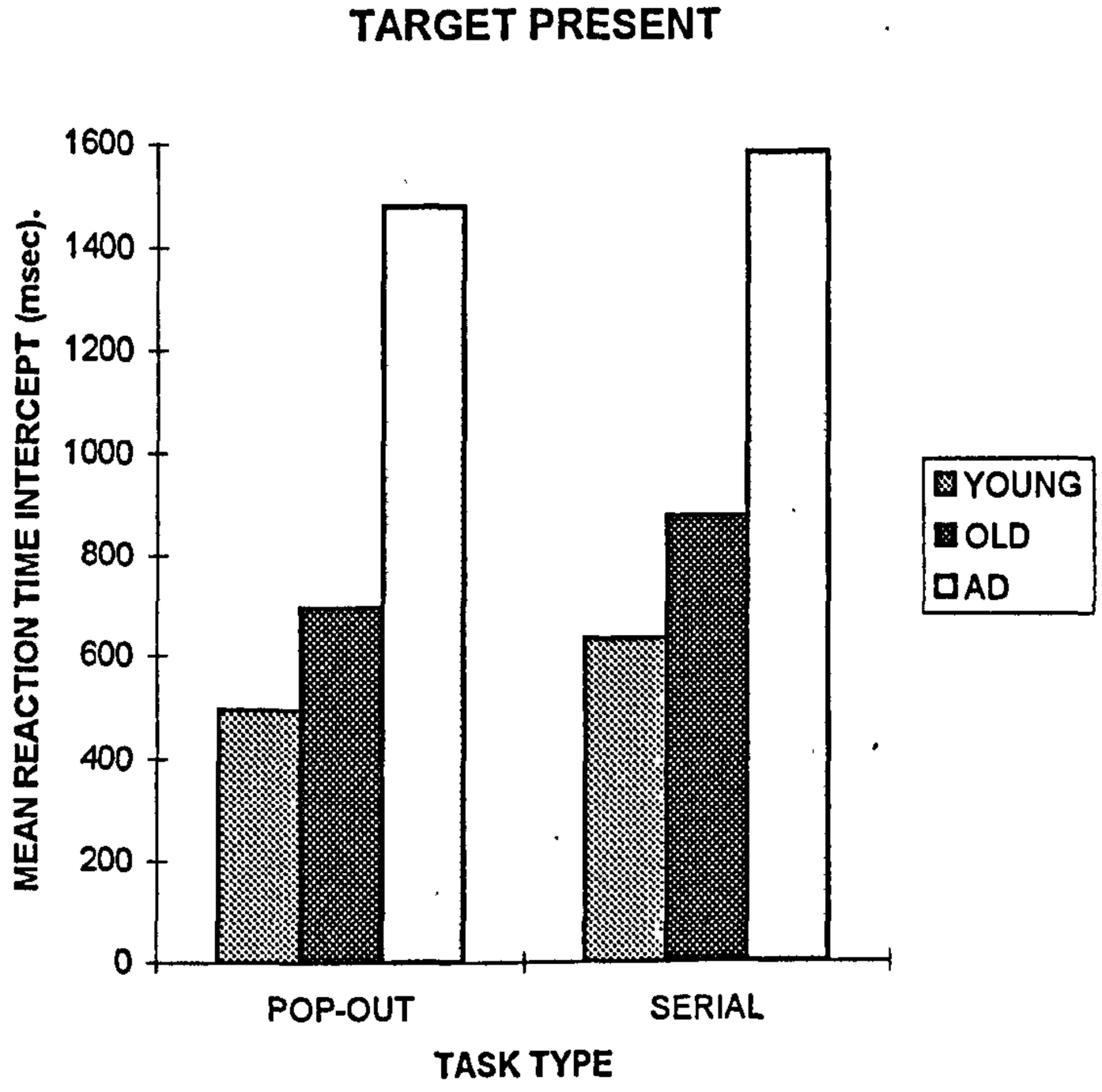
TABLE 4. 5

The mean intercept values for the target present condition of the pop-out and serial visual search tasks, for the young, older and AD groups.

	TARGET PRESENT (msec)		
	YOUNG	OLD	AD
POP-OUT	495.3 sd=50.8	696 sd=100.7	1479.4 sd= 1195.1
SERIAL	632.7 sd=131.3	874.3 sd=143.2	1583.3 sd=939.9

GRAPH 4. 7

The mean values for the intercept values for the target present condition, for the pop-out and serial visual search tasks, for the young, older and AD groups.



For all three groups the serial task resulted in a greater intercept value than for the pop-out task. For the pop-out task older adults had a greater intercept value than younger adults and the AD group had a greater intercept value compared to the older group, a pattern also evident for the serial task.

A two factor, one within and one between subjects ANOVA performed on the target present condition for the intercept values for pop-out and serial search for the three groups indicated that there was no significant main effect of either group, F (df 2,12) = 2.944, $p>0.05$ or visual search task, F (df 1,12) =1.316, $p>0.05$ and no significant interaction between group and task, F (df 2,12) =0.031, $p>0.05$. So although both the pop-out and serial tasks suffered both age related and even greater AD-related deficits these differences failed to reach significance.

TARGET ABSENT DATA

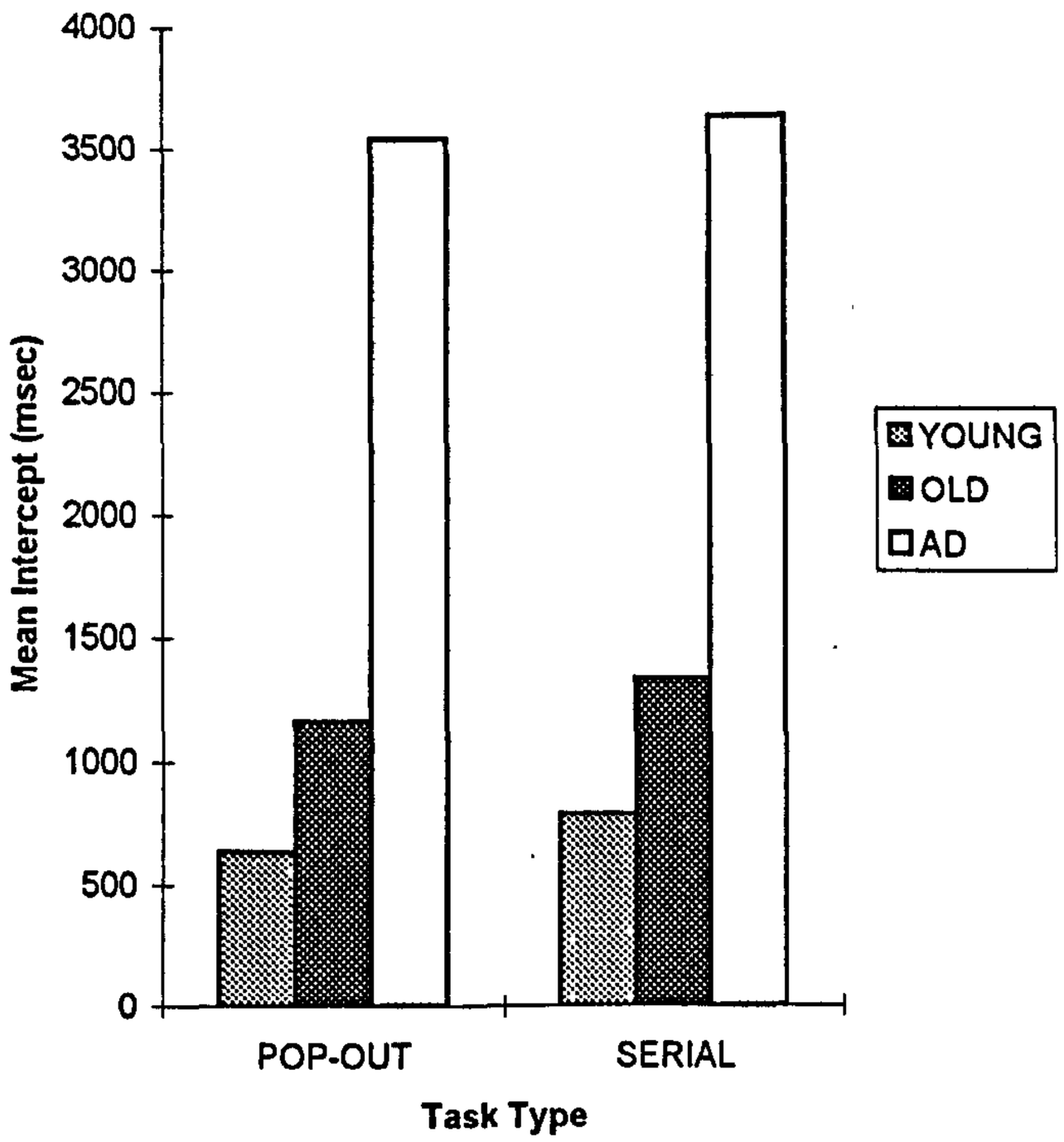
TABLE 4. 6

The mean intercept values for the target absent condition of the pop-out and serial visual search tasks, for the young, older and AD groups.

	TARGET ABSENT (msec)		
	YOUNG	OLD	AD
POP-OUT	637.6 sd=48.2	1166.6 sd=511.8	3542.2 sd=2294.8
SERIAL	784.8 sd=92.0	1329.9 sd=315.2	3624.3 sd=2381.0

GRAPH 4. 8

The mean values for the intercept values for the target absent condition, for the pop-out and serial visual search tasks, for the young, older and AD groups.



The serial task elicited a greater mean intercept value compared to the pop-out task for all three groups. For the pop-out task, the older group had a greater intercept value compared to the younger group and

the AD group had a greater intercept value compared to the older group; this pattern of results was also true for the serial task.

The results of a two factor, one within and one between subjects ANOVA performed on the target absent condition of the pop-out and serial tasks, for the intercept results indicated that although there was a significant main effect of group, F (df 2,12) = 5.257, $p < 0.05$, there was no significant main effect for either task, F (df 1,12) =0.465, $p > 0.05$ or interaction between task and group, F (df 2,12) 0.017, $p > 0.05$.

Further analysis indicated a significant difference between the groups of the pop-out task, F=(df 2,20) 5.08, $p < 0.05$. The deficit of the old compared to the young group failed to reach significance, t (df 8) = 2.06, $p > 0.05$, as did that between the older adult and AD group, t (df 8)= 2.02, $p > 0.05$, (there was a significant difference between the young adult and the AD group, t (df 8) =2.53, $p < 0.05$). There was therefore no significant age or AD-related changes in the target absent condition intercept values for the pop-out task.

Further analysis revealed a significant difference between the groups for the serial task, F (df 2,20) =4.819, $p < 0.05$. The difference in intercept between the young and the older adult groups reached significance, t (df 8)=3.32, $p < 0.01$; the difference between the older adult and the AD group, however failed to reach significance, t (df 8) = 2.02, $p > 0.05$, (there was also no significant difference between the AD and younger adult group, t (df 8) = 2.13, $p > 0.05$). The target absent intercept data was able therefore to indicate a further significant age-related effect.

4.9 (iv) PERCENTAGE (%) CORRECT RESPONSES DATA

TARGET PRESENT DATA

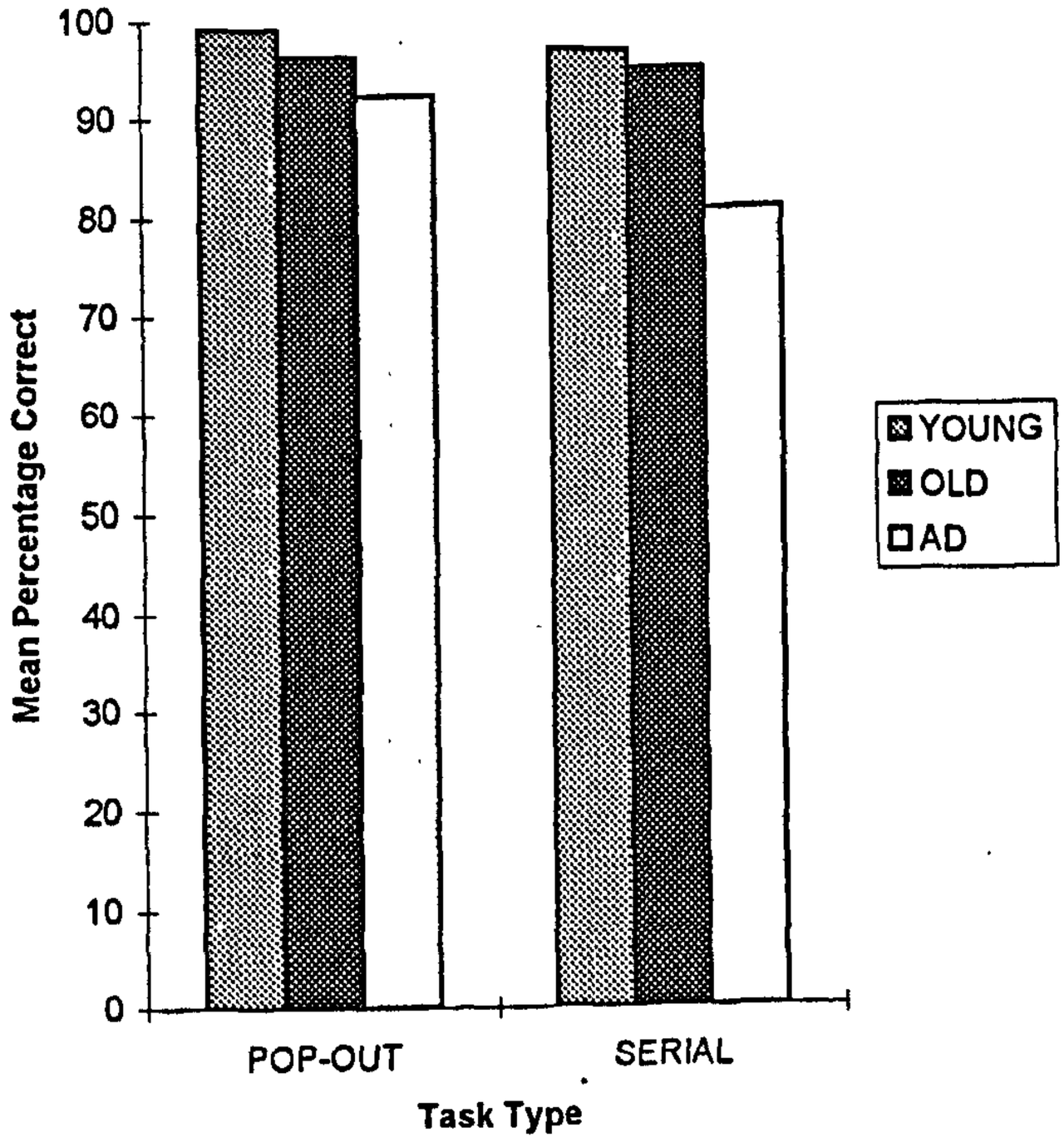
TABLE 4.7

The % correct values, collapsed for all the number of item conditions, for the target present condition for the pop-out and serial search tasks for the young, older and AD groups, (the raw data for the % correct values can be found in tables A4.13 (A- L of the chapter four appendix).

	TARGET PRESENT (% correct responses)		
	YOUNG	OLD	AD
POP-OUT	99.11 sd=1.76	96.4 sd=2.27	92.4 sd=9.4
SERIAL	96.9 sd=2.3	95.1 sd=3.6	80.9 sd=7.9

GRAPH 4.9

The mean % correct values, collapsed for all the items, for the target present condition for the pop-out and serial search tasks for the young, older and AD groups.



A greater percentage of correct responses for the pop-out than for the serial task was apparent for all three groups. For the pop-out task, the older group had more incorrect responses than the young group and the AD group had more incorrect responses than the old group; this pattern was repeated for the serial task.

The results of a two factor, one within and one between subject ANOVA of the % correct data for the target present condition of the pop-out and serial search indicated that there was a significant main effect of both group , $F(df\ 2,12) = 9.434$, $p<0.005$ and task, $F(df\ 1,12) = 5.378$, $p<0.05$; but there was no significant interaction between task and group, $F(df\ 2,12) = 2.275$, $p>0.05$.

Although there were both age and AD-related deficits in the number of correct responses in the pop-out task these differences failed to reach significance, $F(df\ 2,20) = 1.528$, $p>0.05$. There was however a significant difference between the groups for the serial task, $F(df\ 2,20) = 10.465$, $p<0.01$. Although the difference between the young and the older adults failed to reach significance, $t(df=8) = 0.83$, $p>0.05$, the difference between the older adult and AD group, did reach significance, $t(df\ 8) = 3.28$, $p<0.01$

thereby indicating a significant AD-related deficit, one that occurs in addition to what happens in normal ageing. (There was also a significant difference between the AD and the younger adult groups, t (df 8) = 3.47, $p < 0.05$). Importantly, the comparison of the mean reaction time data and the percentage correct responses for all groups revealed no influence on the results from speed accuracy trade off effects.

TARGET ABSENT DATA

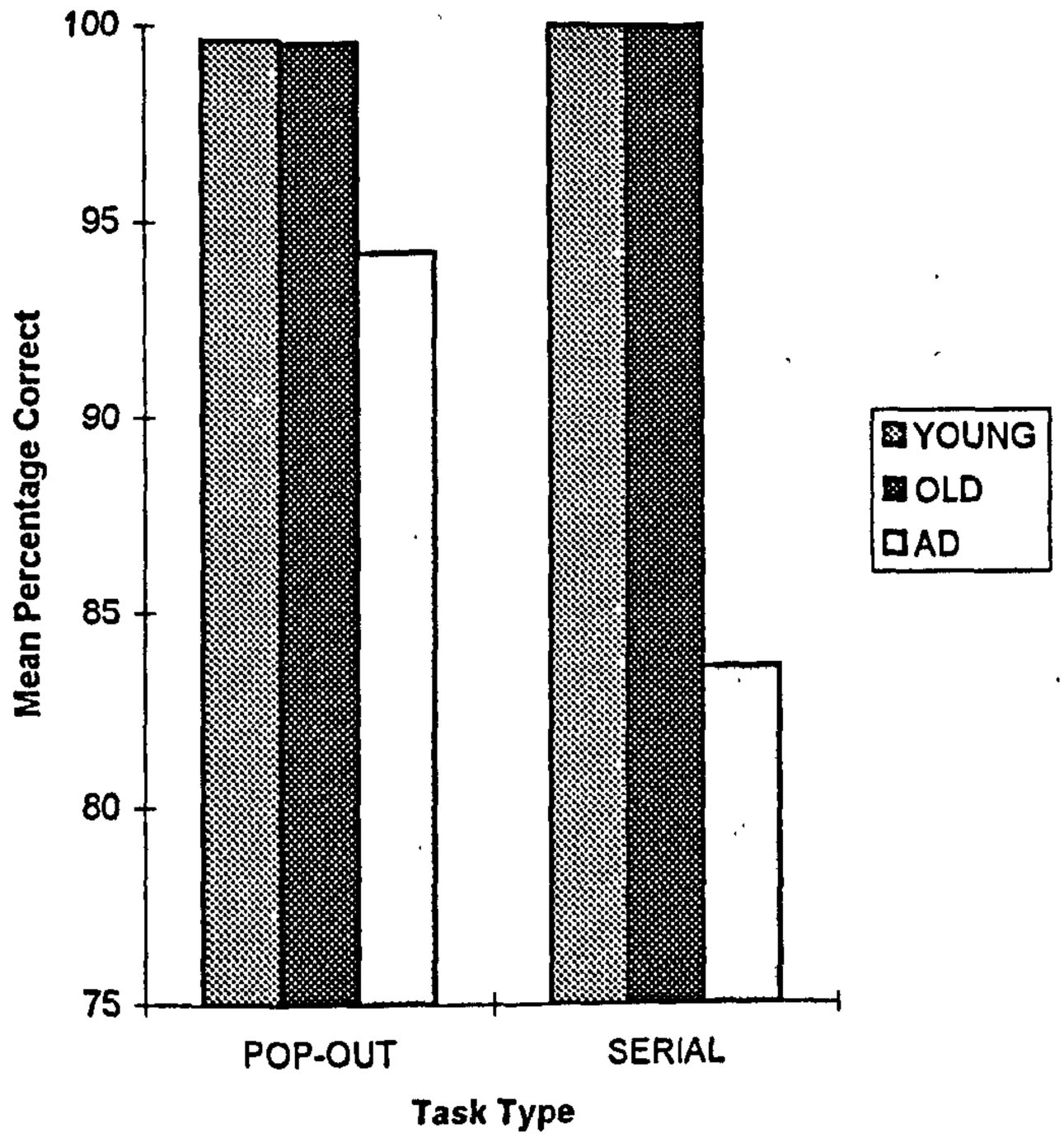
TABLE 4.8

Illustrates the % correct values, collapsed for all the distractors, for the target absent condition for the pop-out and serial search tasks for young adults, older adults and adults with AD.

	TARGET ABSENT (% correct responses)		
	YOUNG	OLD	AD
POP OUT	99.6 sd=0.88	99.55 sd=0.88	94.24 sd=9.47
SERIAL	100 sd=0	100 sd=0	83.6 sd=13.1

GRAPH 4.10

The mean % correct values, collapsed for all the distractors, for the target absent condition for the pop-out and serial search tasks for young, older and AD groups.



For both the young and old groups there was no difference in the percentage correct response between the pop-out and serial task. For both the pop-out and serial tasks, the young and old groups had a greater percentage correct response than the AD group. For the AD group there was a greater percentage correct response in the pop-out compared to the serial task.

The results of a two factor, one within and one between subjects ANOVA applied to the target absent data for the pop-out and serial visual search tasks for the young adult, older adult and AD groups indicated a significant main effect of group, F (df 2,12) = 4.983, $p<0.05$, but no significant main effect of task, F (df 1,12) = 2.667, $p> 0.05$ and no significant interaction between the task and groups, F (df 2,12) =3.434, $p>0.05$.

Further analysis indicated that for the pop-out task there was no significant difference in % correct responses between the groups, F (df 2,20) = 0.864, $p>0.05$. There was however a significant difference between the groups for the serial task, F (df 2,20) = 8.251, $p< 0.01$. As can be seen from the raw data and mean values, there was no difference between the young and older adult groups who both scored

100% correct responses, There was a significant difference between the older adult and the AD group, t (df =8) =2.5, $p < 0.05$ indicating a significant deficit in responding correctly in AD, (there was no significant difference between the AD and younger adult groups, t (df 8) = 2.24, $p > 0.05$).

4.10 DISCUSSION OF THE RESULTS

4.10 (a) TARGET PRESENT POP-OUT RESULTS

According to the measure of the extent to which reaction time increased as a result of the increase in the number of distractors surrounding the target, (i.e., the slope value) although some age-related reduction in the efficiency of automatic visual processing (as measured by pop-out) was apparent, these changes failed to reach significance. The greater decrement in pop-out processing in AD compared to normal ageing also failed to reach significance. It appeared therefore that both ageing and AD were characterised by the sparing of automatic visual target detection, as predicted and as found in previous studies by Oken et al. (1994) and Greenwood et al. (1997).

However, the distinct increase in the time taken to detect the target occurring for the AD group at the 81-distractor level compared to the older adult group, indicated that individuals with AD, unlike those who are ageing normally, may suffer a reduction in automatic target detection when the target is surrounded by very large numbers of distractors. It may be the case that beyond a certain number of distractors, the visual system in AD cannot process the information automatically and has to resort instead to a more serial and therefore more inefficient type of search in order to detect the target. Several other researchers have described how individuals with AD have some problems with screening out irrelevant or distracting stimuli compared to healthy older adults (for example, Sullivan et al., 1995 and Balota and Ferraro, 1993); the results of the present study may therefore be a further indication of this phenomenon.

Effects due to the phenomenon of 'crowding' must also be considered. Crowding results in the poorer visibility of an individual item in a cluttered scene compared to that item on its own (Stuart and Burian, 1962 in Troscianko and Calvert, 1993). The increase in reaction time with the increase in item number from 36 to 81 in AD may also have been the result of an AD-related increase in the effects of crowding compared to older adults. For some reason individuals with AD may be more susceptible to the effects of crowding. Because of the very limited time available to test individuals with AD, experiments controlling for the effects of crowding (see Troscianko and Calvert, 1993) could not be performed in the present study. It would be important in future experimentation to specifically determine the effects of

crowding in AD[193]. Such crowding effects, if present may reduce the saliency of the target, a factor already known to affect the efficiency of visual search (Wolfe, 1994; Nothdurft, 1991, 1993).

The incidental finding that for the target present condition of the serial task that the old and young adults could in fact perform target detection by pop-out rather than by serial search whereas the AD group had to resort to serial search also indicated that automatic visual processing may not be as efficient in AD as in normal ageing.

It may be the case therefore that although the striate cortex is spared in AD in relation to other cortical areas, it may still undergo sufficient change to affect the functions, i.e., automatic visual processing, associated with this area. The indication that there may be some reduction in automatic visual processing in AD compared to normal ageing from this visual search study support the findings from the previous study looking at Visual mismatch negativity in which detriments in some aspects of automatic visual processing in AD compared to normal ageing were also found.

Further studies are of course required in order to determine whether the results of the present study can be repeated and if so, to determine at what concentration the number of distractors begins to affect the time taken to find the target, i.e., the efficiency of pop-out in AD compared to normal ageing.

4.10 (b) TARGET PRESENT SERIAL CONJUNCTION SEARCH RESULTS.

Although some decrement in serial visual search processing did occur with age, the difference in the present study failed to reach significance[194]. The results of the present study did not therefore support the results from previous similar studies which had found significant age-related decrements in serial search (e.g., Plude and Doussard-Roosevelt, 1989; Madden et al., 1996).

When however the serial search performance in AD was compared to that in normal ageing, the AD-related deficit was significant. In comparison to normal ageing, Alzheimer's disease appeared therefore to result in a greater deficit in attention-related target detection[195]. This result agrees with the findings by Oken et al. (1994) and Greenwood et al., (1997).

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[193] This may be of particular importance as crowding is thought to be mediated by the striate cortex and may therefore be a further potential indicator of how AD affects the visual processing associated with this area.

[194] Possibly as a result of the small number of participants in the present study and also the variance in the results between individuals.

[195] It has been suggested that the AD-related decrements in serial search may be the consequence of damage to the attention shifting mechanisms and/or to alterations in the strategies of attention allocation. According to Looren and De Jong et al. (1988) older adults are deficient in the top-down

The reduction in the efficiency of general stimulus processing as illustrated by the intercept and percentage correct data found in the present study, although not statistically significant, support the results of previous studies which have found deficits in the more cognitive aspects of processing, such as increased processing time and problems in decision making, memory formation and retrieval and response accuracy in ageing and to a greater extent in AD.

The results of the present study also indicated that the measurement of target absent responses could also reveal some age and AD-related deficits in automatic and serial processing. Such results may denote that different processes are used for the detection of target presence and absence and that they may be differentially affected by both ageing and AD.

A further finding from the present study was the lack of a significant difference between the slope values of the conjunction serial task and the pop-out task for young adults. Although the conjunction task was designed to produce a serial-type search, the slope values were in fact small; indicating efficient target detection. It appeared therefore that the conjunction task, instead of providing a task which depended heavily on the serial application of visuospatial attention, was in fact a task (similar to those described by Wolfe,1994), in which guided search and therefore efficient target detection, was possible. It is likely that some automatic segmentation at a featural level could have taken place; parsing the field into different, i.e., black or white groups of items, which could then have been used to guide search more efficiently (see Theeuwes, 1994 and Wolfe, 1994). However the finding of a decrement in this processing for the AD group may indicate that the system that guides attention to the relevant location or which signals the output of automatic processing, is detrimentally affected by AD.

Because the conjunction task used in the present study appeared to require relatively little in terms of attentional demand in normal individuals it was not an appropriate task with which to attempt to illustrate age and AD-related deficits in attention-related processing. A task with a greater attentional demand may have been better at illustrating attention-related deficits. Consequently a further study was performed with what was intended to be a visual search task that required a greater attentional demand than the conjunction task.

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memory driven control of attention (i.e., where memory is required to determine the location and identity of the target). So considering the additional memory problems associated with AD (see Lezak, 1995 for a review) one would expect even greater deficits in such processing in AD compared to normal ageing.

4.11 STUDY TWO

Several factors have been identified that are able to affect the extent to which the serial application of visuospatial attention is required to detect a target (Treisman and Gormican, 1988; Duncan and Humphreys, 1989 and Wolfe, 1994). One of these factors is the saliency of the target compared to the distractors.

The aim of study two was to use this 'target saliency' effect in an attempt to increase the attentional demand required for target detection. It was hoped that by increasing the attentional requirement of the visual search task (compared to the conjunction serial search task used in study one) any decrements in attention-related processing in both ageing and AD would be emphasised.

The results from several previous studies have indicated that simple feature target detection can be inefficient, (i.e., demand more attention) if the difference between the target and distractors is subtle (see Wolfe, 1994, for a review). For example, if both the target and distractors are vertical black bars, when the target is significantly larger than the distractors and therefore very salient, pop-out occurs[196]. If however the difference in size between the target and distractor bars is small the lack of target saliency leads to the necessity for serial, attention-demanding search in order to determine its presence[197].

The target in the second task was designed therefore to have only a small difference from the distractors therefore making search for its presence attention-demanding, i.e., serial in nature. Both the targets and distractors were vertical black bars with the target only slightly larger than the distractors (a size serial search task). It was hoped that by using such a subtle difference in size, i.e., in a single feature, guided search would be unlikely to occur. It would not be possible to parse the distractors into separate groups and to perform a search just through a portion of them (as may have happened in the conjunction search). Search would instead have to cover all the distractors.

In addition to performing the size serial search task, participants also performed the conjunction serial task from study one. This was done in order to compare the results of the conjunction and size task and also to determine whether by using a larger sample of people the results of the conjunction task in study two differed from the results of the conjunction task in study one.

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[196] Small differences in colour and orientation between targets and distractors have also been found to result in the need for serial search (Wolfe, 1994).

[197] The reason behind this saliency effect is not clear. However, the very small difference between the target and distractors may mean that target detection has to rely to a greater extent on top-down processes as the target is not sufficiently salient for its presence to be signalled automatically.

The predictions for study two were:

1) Over all groups, the slope values for the size serial search task would be greater than those for the conjunction serial search task.
2) Age-related deficits would be seen for both types of serial search but the decrements would be greater for the size task compared to the conjunction task.
3) Greater deficits would be seen for AD compared to normal ageing for both the size and conjunction task.

4.12 METHOD

PARTICIPANTS

The original aim of the study was to test three groups of individuals; young adults, older adults and older adults with Alzheimer's disease. However, those individuals who formed the AD-group in study one were, even after repeated trials and practice all unable to perform the size task[198]. These individuals were responding correctly to the presence of the target only at chance levels, with almost all of the trials running out of time without a response being made. It was unfortunately not possible to recruit any further individuals with AD. The study was restricted therefore to determining age-related changes in such visual processing; the information from which could then be used for later comparisons with those changes occurring in AD.

There were 25 individuals in the young adult group (8 female, 17 male, with a mean age of 32.6 years; range 20-48) and 25 individuals in the older adult group (15 female, 10 male, with a mean age of 63.4 years; range 50-79). The individuals in both groups were recruited from the general public and the staff and student population of the University of Bristol. Payment was not offered for participation. All participants had normal or corrected to normal vision[199]. In addition the participants had no known neurological disorder and were not taking prescribed medication.

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[198] The reason for the inability of the individuals with AD to perform the size task was unclear. There was the possibility that the description of the target in terms of size was a more difficult concept to understand, recognise or remember. Individuals with AD may have had particular problems in discriminating very similar stimuli. In addition, the slower rates of information extraction and processing generally found in AD (and also to a lesser extent in normal ageing) may have meant that for the fixed duration (10 sec) of viewing allowed to detect the presence or absence of a target in a given visual scene presentation, there was a decreased probability of identifying a target. As a result, when the individuals responded it may have been in a manner consistent with incompletely encoded [and processed] information, (see Harpur, Scialfa and Thomas, 1995).

[199] All participants were asked about any visual problems and were asked to read out the written instructions for the test and also to describe and discriminate both the target and distractor stimuli; a practice run was also given for each individual to ensure that vision was normal.

4.13 EXPERIMENTAL TECHNIQUE AND STIMULI

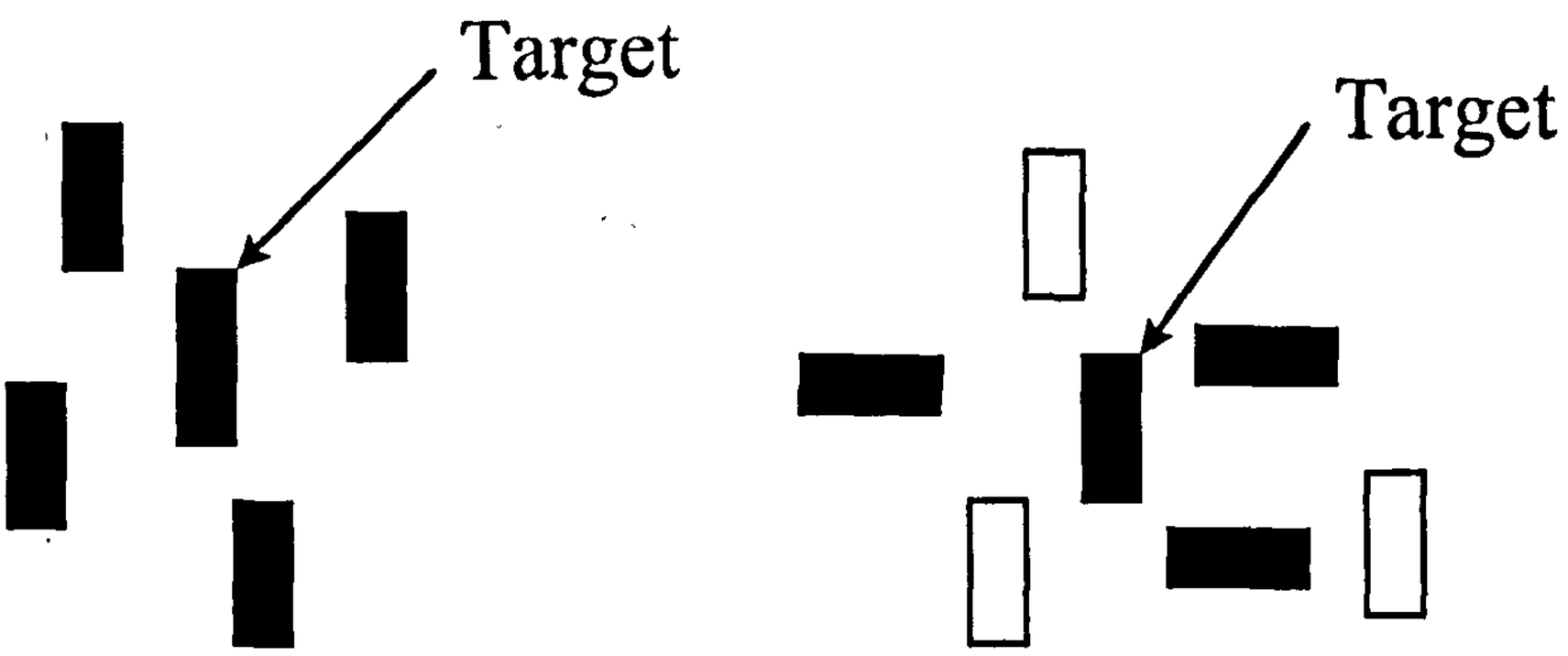
APPARATUS

All testing was performed in a room normally used for cognitive testing, with its normal level of ambient lighting. Only the participant and the experimenter were present. The stimuli were generated on an IBM PC system. The display was presented on a colour monitor on which just the green phosphor was activated. The area used to display stimuli subtended 17.3 x 10.6 degrees at a viewing distance of 80 cm in front of the display monitor so that the eye was at the same height as the centre of the monitor display. The luminance of the uniform green screen was 5.6 cd m^{-2}.

For the conjunction serial search task the luminance of the dark bars was 4.3 cdm^{-2}; the luminance of the light bars was 7.3 cd m^{-2} (giving a Michelson contrast of 13 % for both light and dark stimuli[200]). Each bar subtended 0.3 x 0.7°. In the size serial search task, the target was a single vertical black bar and the distractors were slightly smaller vertical black bars. The target bar subtended 0.3 x 0.7°; the distractor bars subtended 0.24 x 0.56°. The luminance of the dark bars was 4.3 cd m^{-2}. Each bar was located in a grid box but with a random internal pertubation and no bars touched each other. An example of the type of display used in the experiments can be found in figure 4.1.

FIGURE 4.2

The Size (a) and Conjunction (b) Serial visual search task stimuli.



[200] This value was used since a control experiment by Troscianko and Calvert (1993) suggested that the contrast response function was bottomed out at that value and therefore minor changes in perceived contrast would not be expected to affect the results (Weinstein et al 1997).

Response to the presence or absence[201] of the target was indicated by the participant pressing one of two buttons mounted on a hand held box. The buttons were large, easy to press and to hold. The target could appear at any location amid 3 possible arrays of items (16, 36, 81). If a button had not been pushed for more than 10 seconds the computer ignored that trial (but repeated it later); the whole area of the screen tuned green and displayed an 'out of time' message. The run was restarted by pressing one of the buttons. Anticipatory responses of less than 100 msec were also rejected.

For both the conjunction and size tasks the order of stimulus presentation, i.e. target present or target absent, with 16, 36 or 81 distractors were randomly presented. There were 30 trials for each of the six conditions, i.e., 16, 36, 81 items with the target present and 16, 36, 81 items with the target absent. For the actual test no feedback was given about whether the response was correct or not. Reaction time to the detection of the target was recorded as was the percentage (%) of correct responses and stored on disc for subsequent off-line analysis.

PROCEDURE

Participants were seated 80cm away from the centre of the screen. Before data collection commenced participants were shown the apparatus and were given the opportunity to ask questions. After a description of the task requirements the participants were asked to perform a practice trial to ensure that they could understand the task, identify the target and the distractors for each type of visual search task[202] and were able to use the buttons to respond appropriately. Potential participants were excluded if they performed only at chance levels. The participants were told that there would be a target present on only 50% of the trials. The participants were then instructed to fixate on the fixation spot (which appeared at the centre of the screen 100 msec before the onset of each stimulus array) and when the stimuli appeared, to try and detect the target as quickly but as accurately as possible.

The time taken to perform both tasks ranged from 30 to 40 minutes, which task was performed first was counterbalanced and no feedback about performance was provided.

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[201] Target absent responses were included to ensure that participants did not simply respond with a button press even though they had not detected the target.

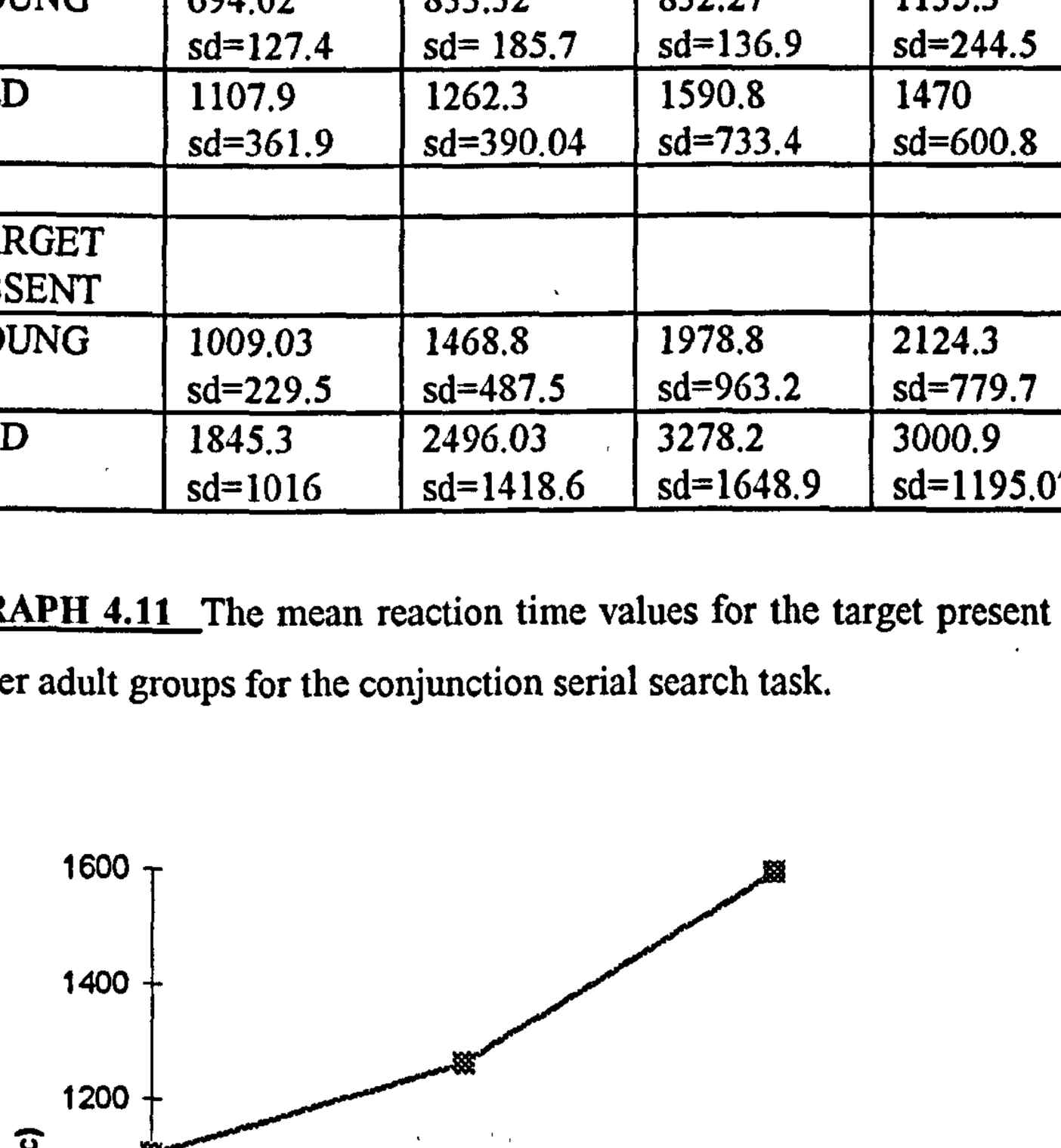
[202] The practice trials for the two visual search tasks were performed separately, each one performed just before the relevant trial, so as to avoid potential confusion.

4.14 RESULTS

TABLE 4.9 The mean reaction time (RT) values for the target present and the target absent conditions for the young and older adult groups for the conjunction and the size serial search tasks. (The raw data can be found in tables A4.14 -4.17 of the chapter four appendix).

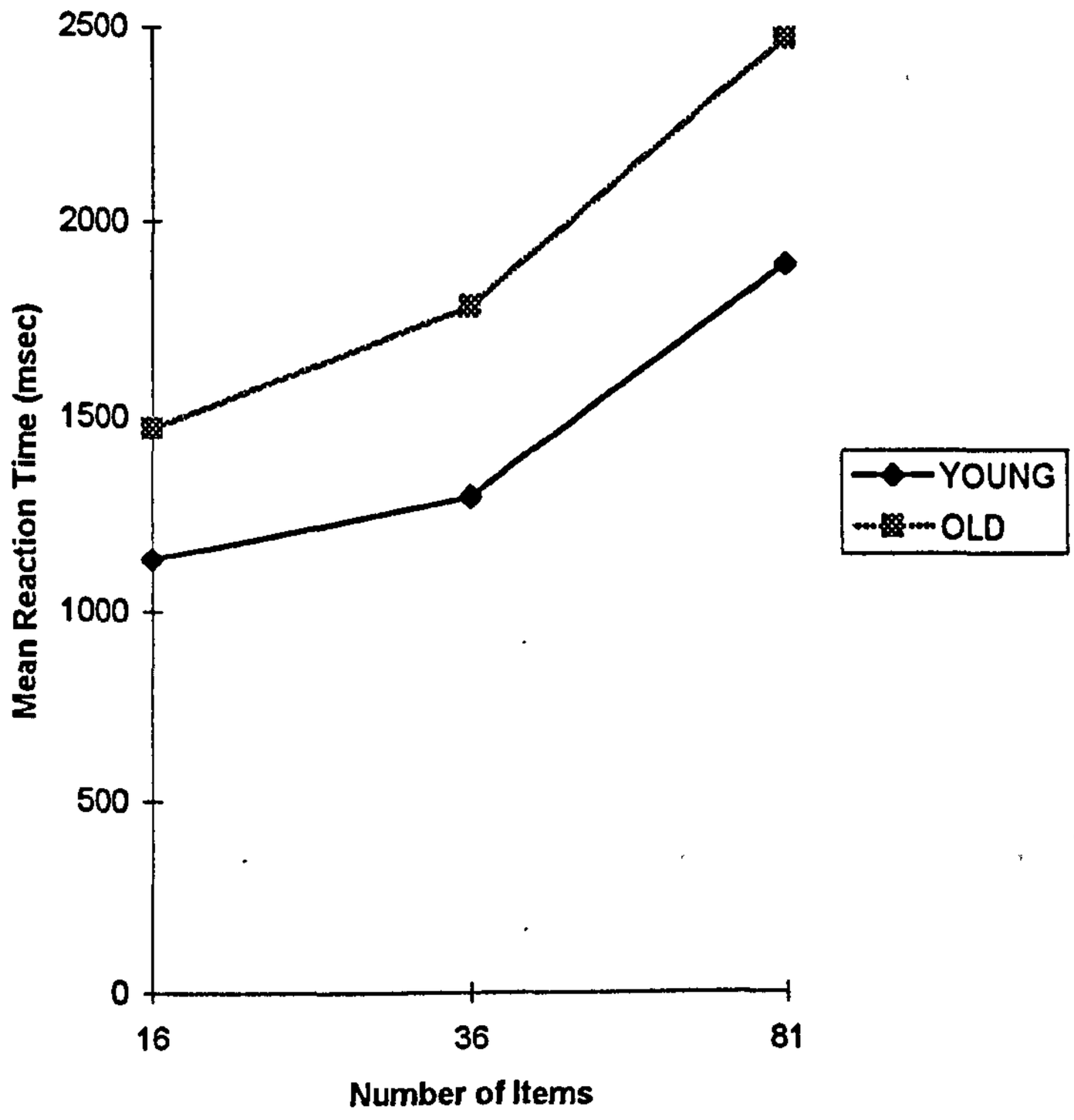
	CONJUNCTION (RT, msec)			SIZE (RT, msec)		
TARGET PRESENT	Number of Items			Number of Items		
	16	36	81	16	36	81
YOUNG	694.02 sd=127.4	833.32 sd= 185.7	832.27 sd=136.9	1135.3 sd=244.5	1295.9 sd=326.5	1883.7 sd=561.8
OLD	1107.9 sd=361.9	1262.3 sd=390.04	1590.8 sd=733.4	1470 sd=600.8	1780.9 sd=822.7	2461.2 sd=929
TARGET ABSENT						
YOUNG	1009.03 sd=229.5	1468.8 sd=487.5	1978.8 sd=963.2	2124.3 sd=779.7	2653.5 sd=1023.5	3231.6 sd=1551.6
OLD	1845.3 sd=1016	2496.03 sd=1418.6	3278.2 sd=1648.9	3000.9 sd=1195.07	3765.2 sd=1446.3	4807.6 sd=1664.4

GRAPH 4.11 The mean reaction time values for the target present conditions for the young and the older adult groups for the conjunction serial search task.



For the young adults there was an increase in reaction time (RT) with an increase in the number of distractors from 16 to 36; but no further increase with 81 distractors. For the older adults however there was an increase in RT from 16 to 36 and from 36 to 81. The overall RT was greater for the older compared to the young adult group.

GRAPH 4. 12 The mean reaction time (msec) for 16, 36 and 81 items for the target present condition of the size task for young and older adults.



For both the young and older adults there was an increase in RT as the number of distractors increased; with the older adults having the greater RT over all distractor conditions.

Both the conjunction and serial search tasks were largely[203] serial in nature, but the time taken to detect the target in the size condition was greater than the time taken to detect the target in the conjunction task for all distractor conditions for both the young and older groups.

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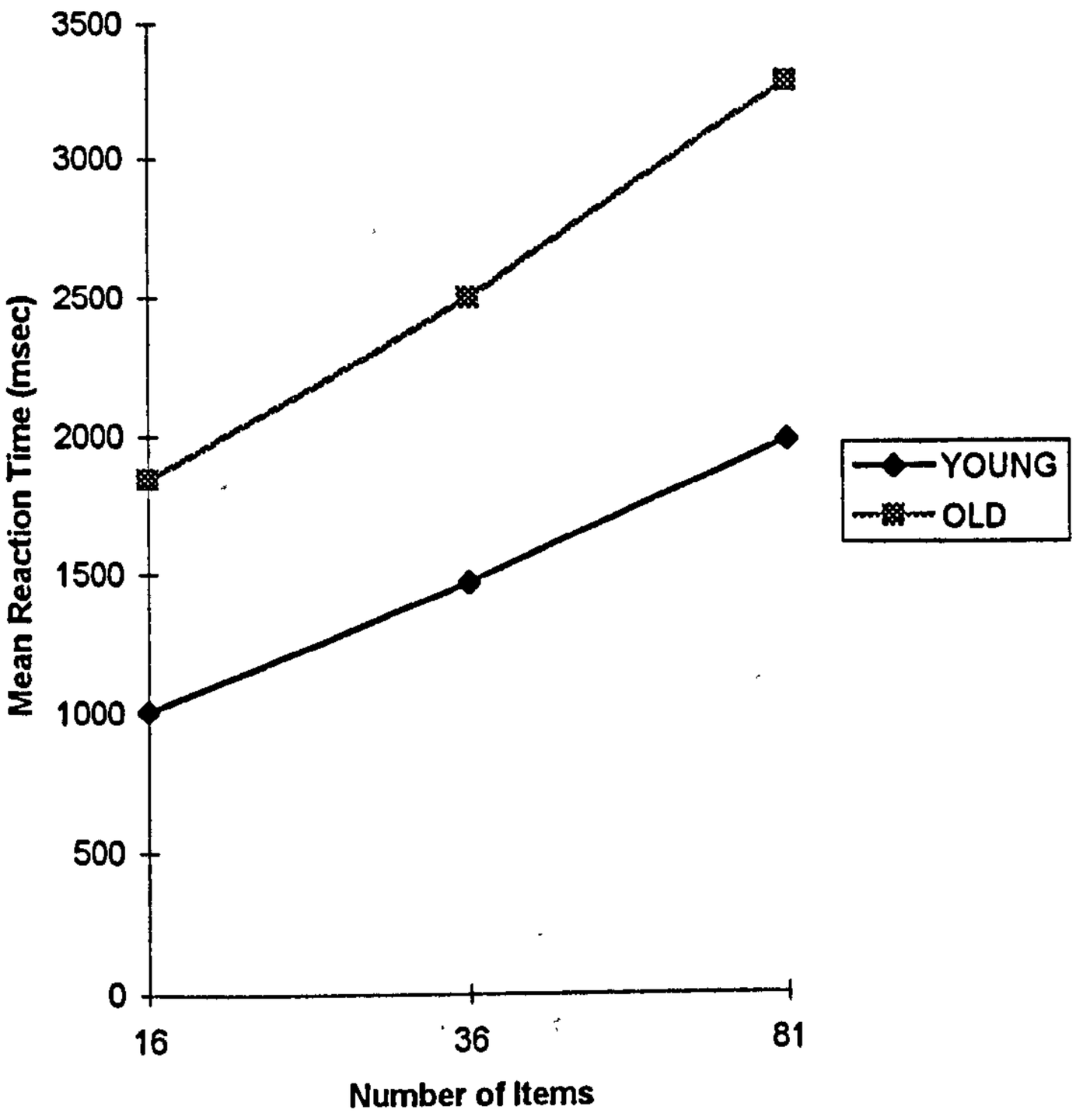
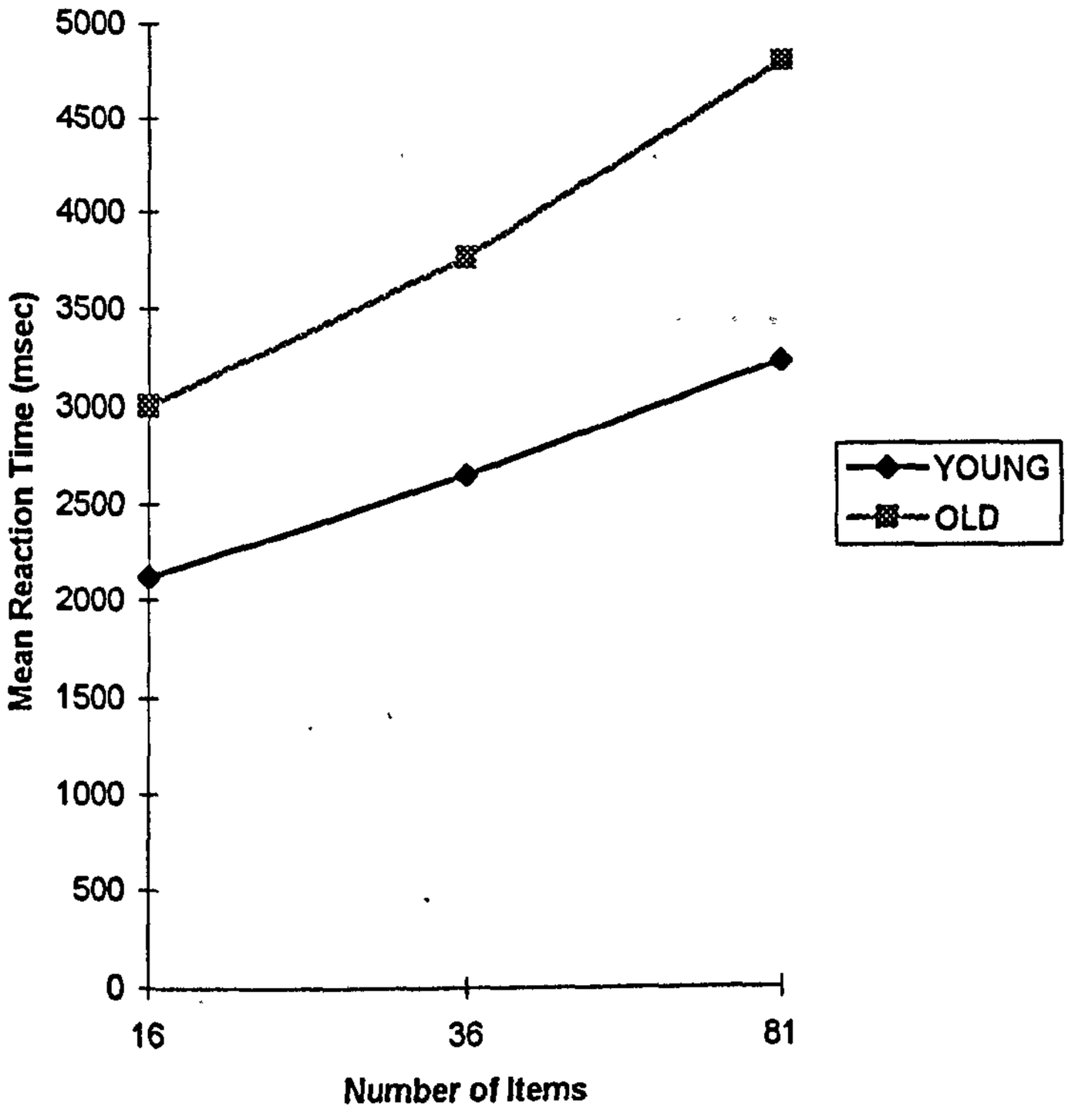
[203] In the target present condition of the conjunction task for the young adults although there was an increase in RT as the distractor number increased from 16 to 36, there was actually a slight decrease in RT when the number of distractors increased from 36 to 81.

GRAPH 4.13 The mean reaction time (msec) for 16, 36 and 81 items for the target absent condition for the conjunction task for young and older adults.



For both the young and older adults there was an increase in RT as the number of distractors increased; with the older adults having the greater RT over all distractors.

GRAPH 4.14 The mean reaction time (msec) for 16, 36 and 81 items for the target absent condition of the size task for young and older adults.



For both the young and older adults there was an increase in RT as the number of distractors increased; with the older adults having the greater RT over all distractors.

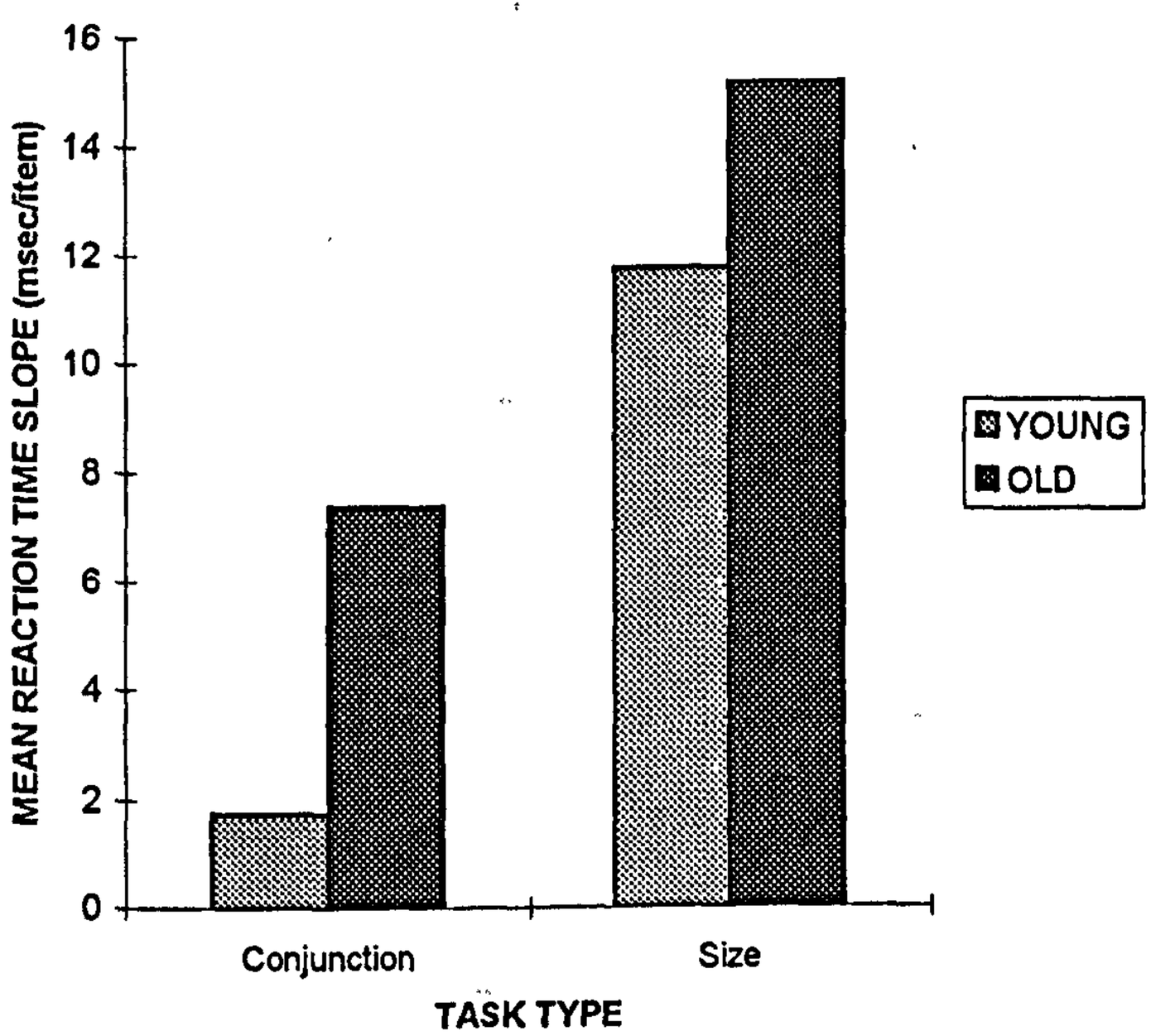
TABLE 4.10

As in study one, linear regression analysis of the mean reaction time necessary to detect the presence or absence of the target when surrounded by 16, 36 and 81 distractors was performed to obtain the mean slope value and the mean intercept value for each experimental condition. The results are displayed in the table below (the raw data is displayed in tables A4.18-4.21 of the chapter four appendix).

	CONJUNCTION SLOPE VALUE (msec/item)		SIZE SLOPE VALUE (msec/item)	
	Target Present	Target Absent	Target Present	Target Absent
Young Adults	1.76 sd=1.8	14.32 sd=12.7	11.78 sd=6.6	16.328 15.3
Older Adults	7.404 sd=7.0	21.25 sd=14.3	15.2 sd=10	26.96 sd=16.9

GRAPH 4.15

The mean RT/ (number of items) slope values for the target present condition for the young and the older adult groups for the conjunction and the size serial search tasks.



The slope values for both the young and older adult groups were greater for the size compared to the conjunction serial visual search task, indicating the greater attentional demand of the size compared to the conjunction task. For both the conjunction and size tasks older adults had the greatest slope values, indicating a reduction in the efficiency of such processing with age.

The results of a two-factor, one within and one between factor ANOVA applied to the target present condition of the slope values indicated a significant main effect of both age, F (df 1,48) = 8.393, p= <0.01 and visual search type, F (df 1,48) =47.033, p<0.01. There was however no significant interaction, F (df 1,48)= 0.712, p= > 0.05.

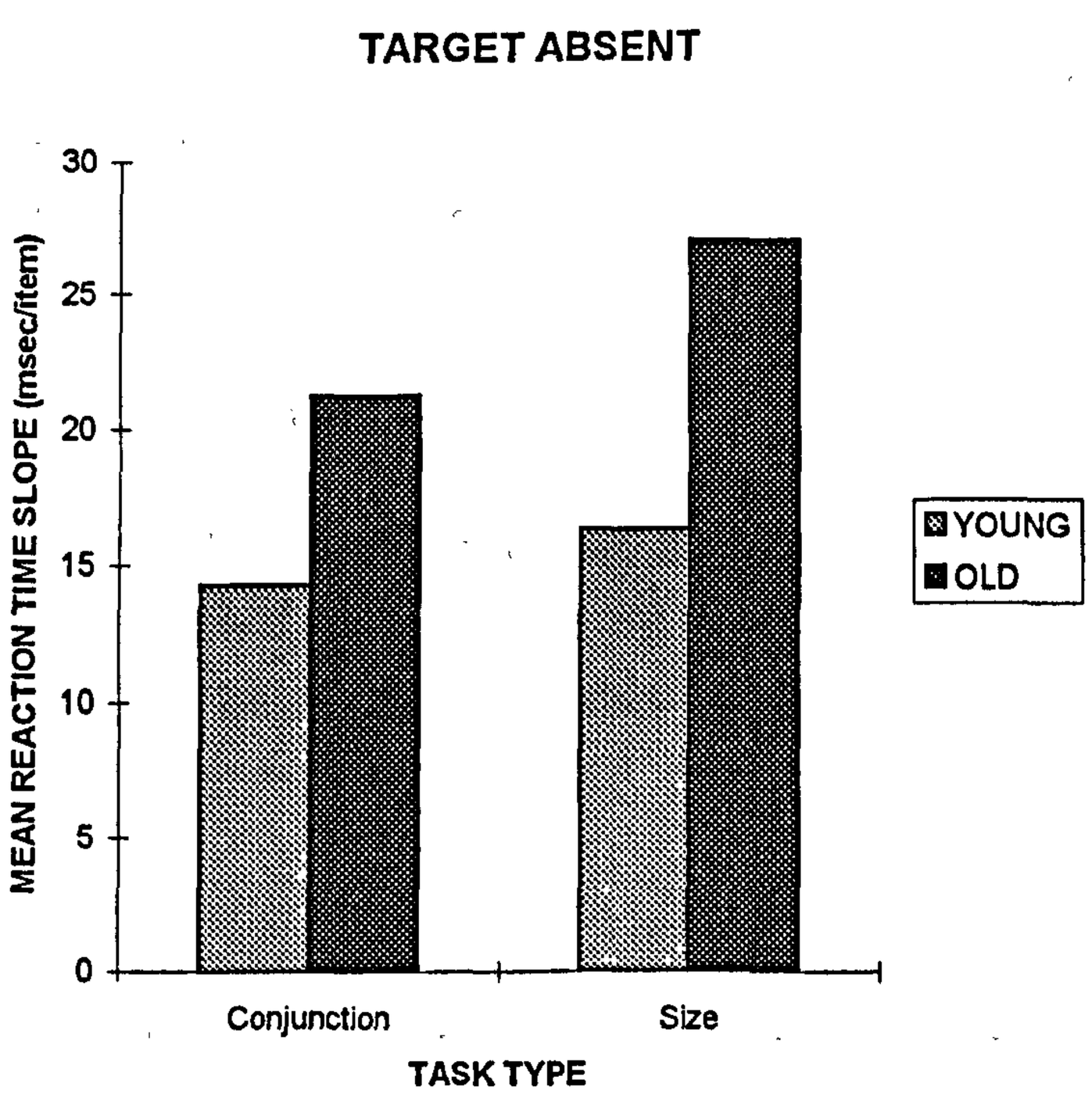
For the young adults the difference in mean slope value between the conjunction and size task reached significance, F (df 1,48) =29.661, p= < 0.001 with the size task having the greater value and therefore demanding greater attention. For the older adults the difference in mean slope value between the conjunction and size task also reached significance, F (df 1,48) =18.08, p= <0.001, with the size task

eliciting the greater value and therefore demanding greater attention. As predicted therefore, the size serial visual search task was more attention-demanding than the conjunction task.

For the conjunction task, the difference in mean slope value between the young and older adult groups reached significance, F (df 1,96) =7.66, p= <0.01, with the older adults having the greater slope value and therefore less efficient processing than the young group. This was the opposite of the results found in the same conjunction task in study one, where there was no significant difference in slope values between the young and older adults.

Although the size task appeared to be more attention demanding than the conjunction task the difference in slope value between the young and older adult groups failed to reach significance, F (df 1,96) 2.861, p= > 0.05. This indicated that the size task even though more attention-demanding in nature did not produce significantly greater age-related decrements than those found for the conjunction task.

GRAPH 4. 16 The mean RT/ distractor number slope values for the target absent condition for the young and the older adult groups for the conjunction and the size serial search tasks.



For both the young and older adults there was a greater slope value for the size compared to the conjunction task. In both the size and conjunction task, older adults had greater slope values than younger adults.

The results of a two factor one within and one between factor ANOVA applied to the slope values of the target absent condition indicated a significant main effect of age, F (df 1,48) 5.837, p= <0.025, but not of visual search type, F (df 1,48) =3.733, p=>0.05 and no significant interaction, F (df 1,48) = 0.616, p>0.05.

Further analysis indicated that the difference in slope value between the young and the older adults for the conjunction task, failed to reach significance, F (df 1,96) =2.952, p>0.05. The difference in slope value between the young and older adult groups for the size task did however reach significance, F (df 1,96) = 6.199, p <0.02.

The results also indicated that for both the young, F (df 1,48) = 0.658, p >0.05 and older adults groups, F (df 1,48) =3.691, p >0.05, there was no significant difference in slope value between the conjunction and the size task.

For the conjunction task although there was a greater slope value for the older compared to the younger adults this difference failed to reach significance. The greater slope value for the older adults compared to the young adults on the size task did however reach significance. This was an opposite pattern of results to those found for the target present condition and indicated therefore that the recording of target absent responses may provide some useful indicators of change in patterns of processing with age.

4.15 INTERCEPT VALUES

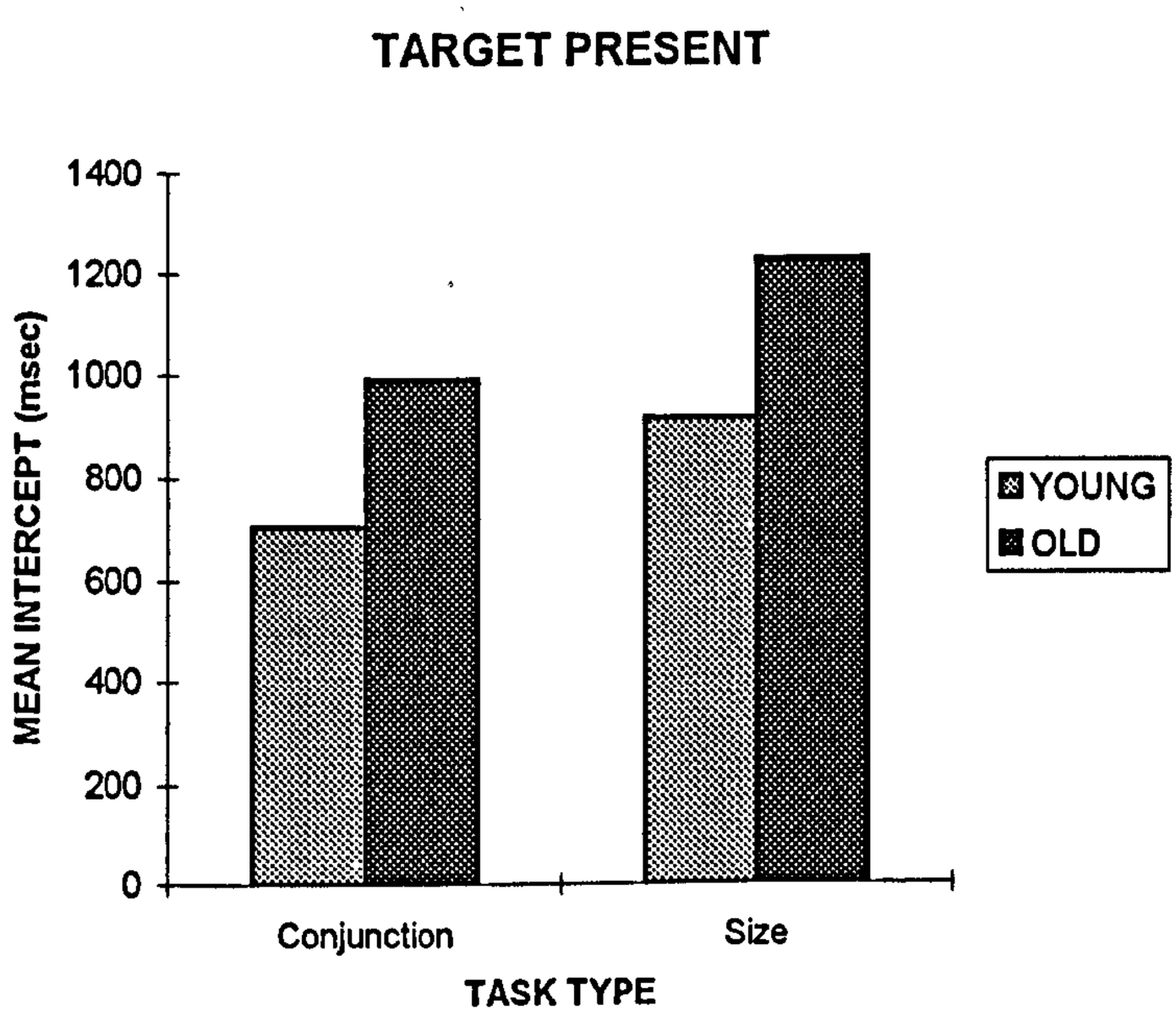
The intercept values arising from the linear regression analysis of the reaction time and distractor results for the target present and target absent conditions of the conjunction and serial visual searches for the young and the older adult group are displayed in table 4.11. (The raw data can be found in tables A4.18-4.21 of the chapter four appendix).

TABLE 4.11

	CONJUNCTION		SIZE	
	Target Present	Target Absent	Target Present	Target Absent
Young Adults	705.996 sd=156.5	851.016 sd=249.9	916.292 sd=239.4	1946.008 sd=681.2
Older Adults	991.916 sd=272.1	1597.456 sd=1035.4	1228.984 sd=657.6	2666.876 sd=1285.1

GRAPH 4.17

The mean intercept values arising from the linear regression analysis of the reaction time results for the target present condition of the conjunction and size serial visual searches for the young and the older adult groups.



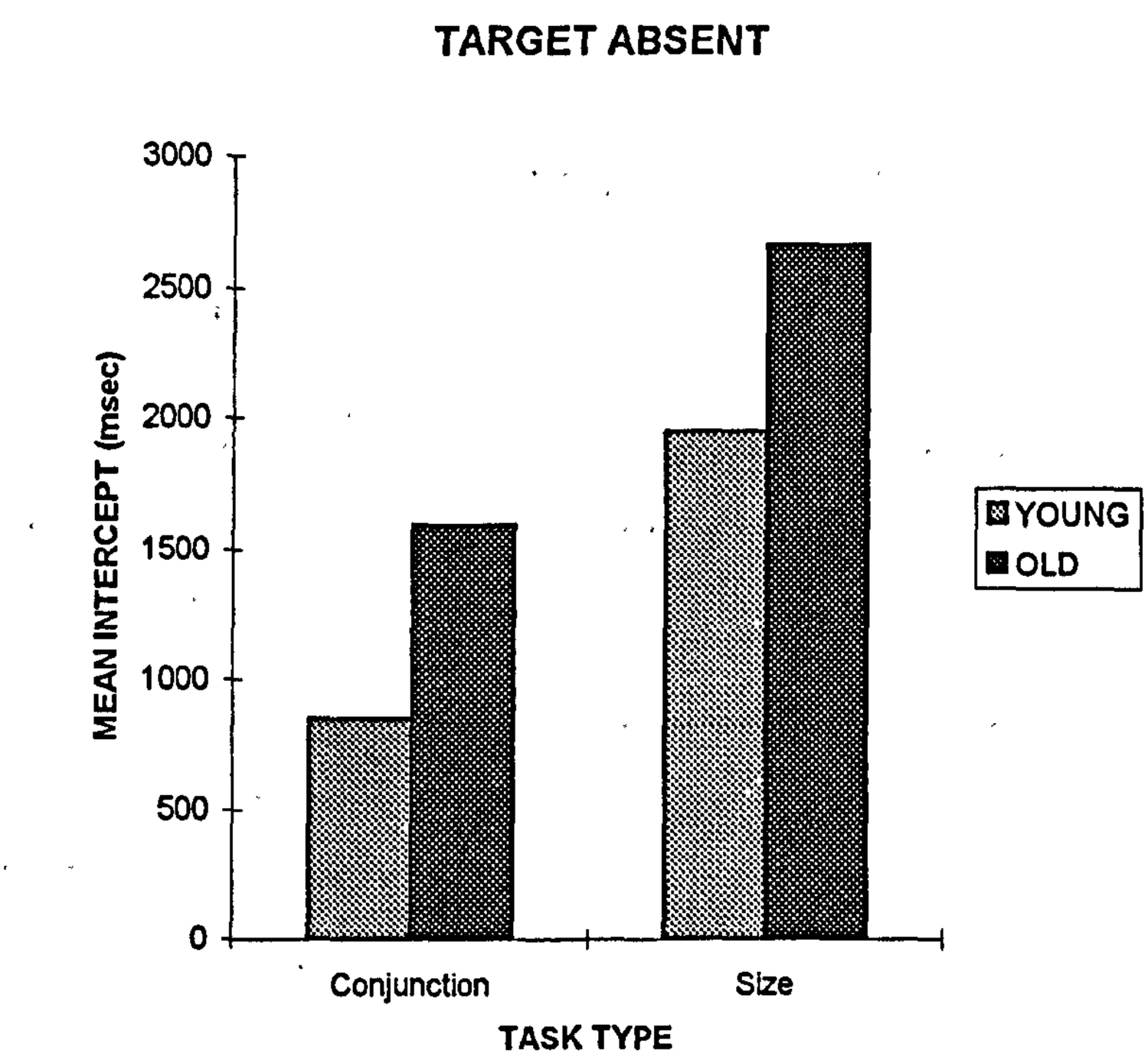
For both conjunction and size tasks, greater mean intercept values were found for older compared to younger adults with the intercept values for both young and older groups greater for the size compared to the conjunction serial task

The results of a two factor one between and one within subjects factors analysis of variance, indicated that for the target present condition there was a significant main effect of both age, F (df 1,48) = 13.736, $p<0.001$ and visual search task, F (df 1,48) = 8.727, $p <0.005$. There was however no significant interaction, F (df 1,48) =0.031, $p >0.05$.

Further analysis indicated that for the conjunction task, the greater intercept value for the older adults reached significance, F (df 1,96) =6.671, $p <0.01$. For the size task, the greater intercept value for the older adults also reached significance, F (df 1,96) =7.978, $p <0.01$, indicating that in both tasks the stimulus encoding, processing and response factors were less efficient with age.

For the younger adult group there was no significant difference in intercept value between the conjunction and the size task, F (df 1,48) = 3.857, p >0.05 indicating that younger adults did not find the processing of the size task much different to that of the conjunction task. There was however a significant difference between the conjunction and the size task, F (df 1,48) =4.901, p <0.05 for the older adult group, indicating that it was more difficult for older adults to process the size task than the conjunction task.

GRAPH 4.18 The mean intercept values arising from the linear regression analysis of the reaction time results for the target absent condition of the conjunction and serial visual searches for the young and the older adult groups.



For both the conjunction and size task the mean intercept values were greater for the older adults. For both the young and older adults the size task resulted in greater mean intercept values than for the conjunction task.

The results of a two factor analysis of variance, one between and one within subjects factors indicated that for the target absent condition of the mean intercept results there was a significant main effect of age, F (df 1,48) = 13.521, p<0.005 and a significant main effect of visual search task, F (df 1,48) =41.978, p <0.001. There was however no significant interaction, F (df 1,48) = 0.006, p>0.05.

Further analysis indicated that for the conjunction task the greater intercept value for the older compared to the younger adults reached significance, F (df 1,96) = 8.229, p <0.01. For the size task, the greater intercept value for the older compared to the younger adults also reached significance, F (df 1,96) = 7.675, p <0.01, indicating therefore a significant age-related decrement in the processing of both tasks.

For the young adult group the difference in slope values between the conjunction and size conditions reached significance, F (df 1,48) =21.488, p <0.001. For the older adults the difference in slope values between the conjunction and size tasks also reached significance, F (df 1,48) =20.496, p<0.001.

These results indicated that the measurement of target absent responses could also provide age-related effects in addition to those of the target present condition.

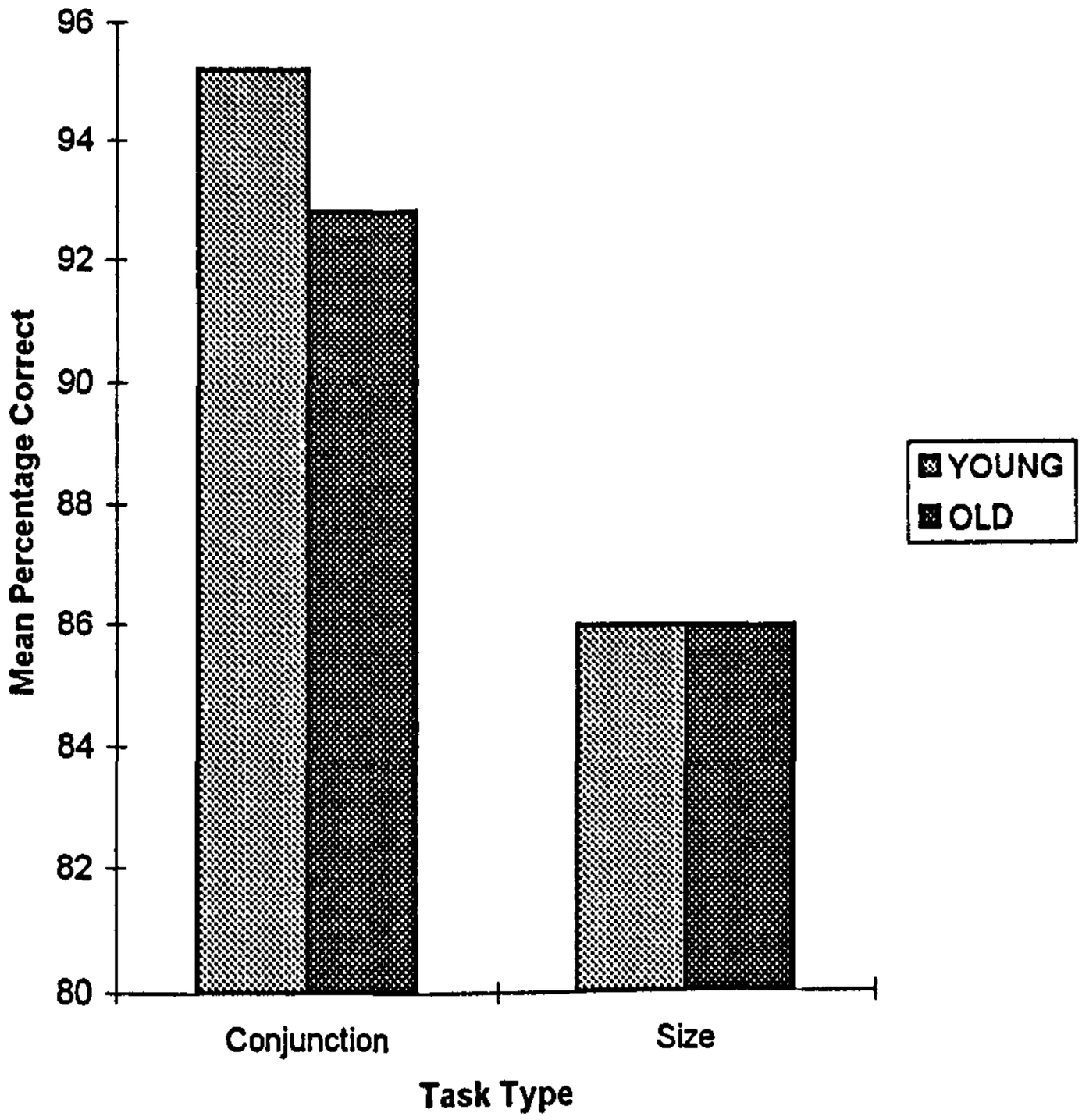
4.16 PERCENTAGE (%) CORRECT RESPONSES

TABLE 4.12

The mean % correct responses for the target present and target absent conditions of the conjunction and size serial visual searches for the young and the older adult groups. (The raw data can be found in tables A4.13-4.16 of the chapter four appendix).

	CONJUNCTION		SIZE	
	Target Present	Target Absent	Target Present	Target Absent
Young Adults	95.2105	99.4211	85.97	96.3895
Older Adults	92.8842	99.3053	85.9632	98.4947

GRAPH 4.19 The mean % correct responses for the target present conditions of the conjunction and size serial visual searches for the young and the older adult groups. The raw data can be found in table A4.14 - A4.17 of the chapter four appendix.



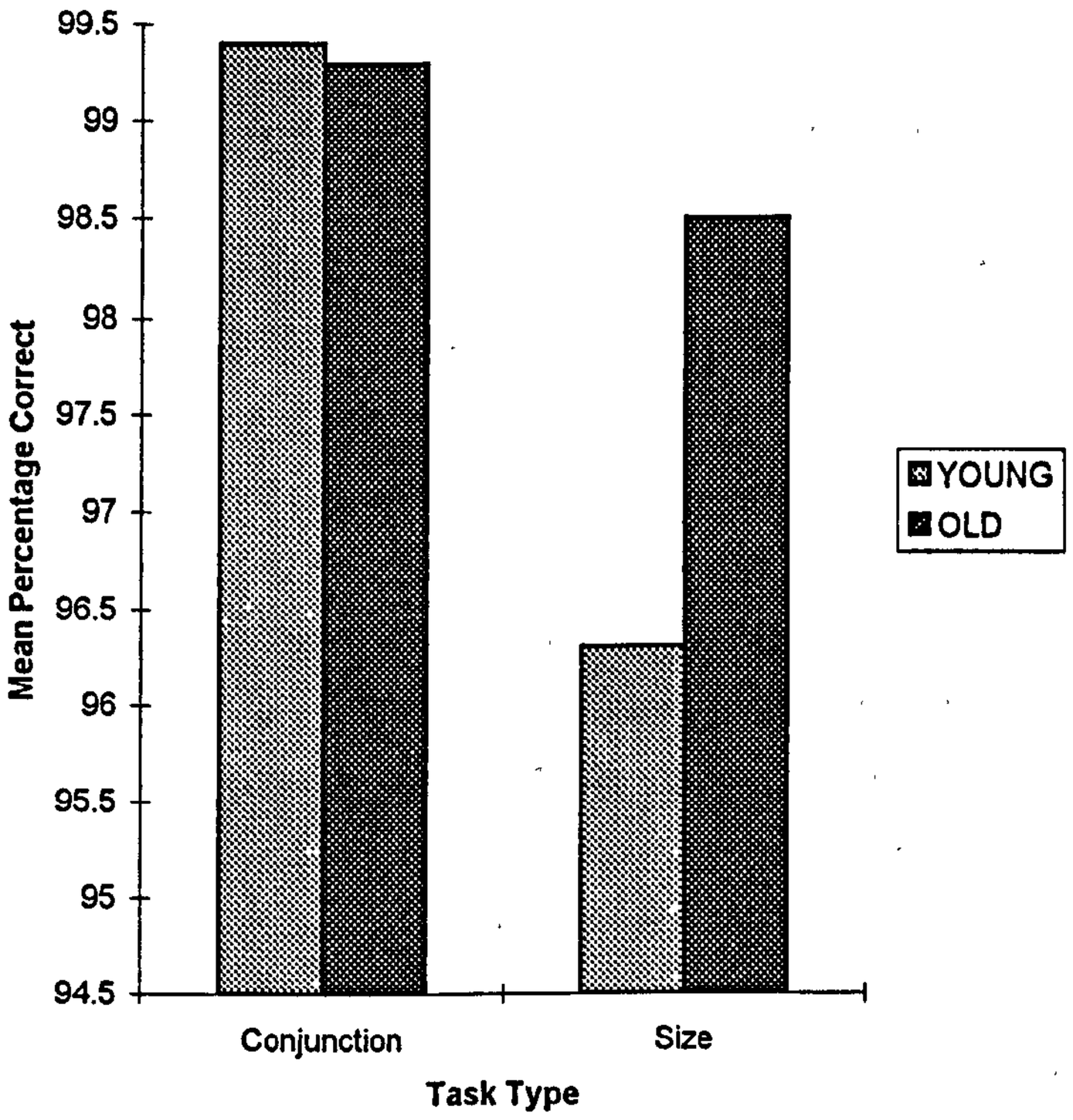
For both the young and old adults the conjunction task resulted in the greater mean percentage correct responses compared to the size task. For the conjunction task younger adults had a greater percentage of correct responses , for the size task young and older adults had the same percentage of correct responses.

The results of a two factor, one within and one between subject ANOVA for the target present data indicated that for the % correct response data there was no significant main effect of age, F (df 1,36) = 0.253, $p > 0.05$. There was a significant main effect of visual search task, F (df 1,36) = 25.669, $p < 0.001$. There was no significant interaction, F (df 1,36) = 0.529, $p > 0.05$.

Further analysis indicated that for the conjunction task the difference in percentage correct responses between the young and older adults failed to reach significance, F (df 1,72) =0.683, $p > 0.05$. For the size task the difference in percentage correct responses between the young and older adults also failed to reach significance, F (df 1,72) =0, $p > 0.05$. The percentage correct response therefore proved of little value in illustrating age-related effects.

For young adults, the difference in percentage correct responses between the conjunction and size task reached significance, F (df 1,36) =16.785, p <0.001. For older adults the difference in percentage correct responses between the conjunction and size task reached significance, F (df 1,36) = 9.413, p <0.005.The comparison of reaction time and percentage correct responses indicated no evidence for speed accuracy trade off effects within the results.

GRAPH 4.20 The mean % correct responses for the target absent conditions of the conjunction and size serial visual searches for the young and the older adult groups.



For both young and older adults a greater mean percentage correct response was obtained in the conjunction than for the size task. For the size task older adults had a higher percentage correct response than the older adults; in the conjunction task the values for the young and older groups were very similar.

The results of a two factor, one within and one between subject ANOVA for the target absent data indicated that for the % correct response data there was no significant main effect of age, F (df 1,36) = 1.606, p= >0.05. There was however a significant main effect of visual search task, F (df 1,36) = 6.9, p <0.025; there was no significant interaction, F (df 1, 36) = 2.306, p >0.05.

Further analysis indicated that for the conjunction task, there was no significant difference in % correct between the young and the older adult groups, F (df 1,72) = 0.012, p >0.05. For the size task there was also no significant difference in % correct between the young and the older adult groups, F (df 1,72) = 3.851, p>0.05. For the young adult group the difference between the conjunction and the size task in percentage correct responses reached significance, F (df 1,36) =8.592, p<0.01. For the older adult group the difference between the young and older adults in the percentage of correct responses, failed to reach significance, F (df 1, 36) =0.614, p= >0.05.

4.17 DISCUSSION OF THE RESULTS OF STUDY TWO

4.17 (a) THE CONJUNCTION SERIAL SEARCH TASK

In contrast to the findings of study one, the target present condition of the conjunction task in study two did reveal a significant age-related deficit. The slope values were significantly greater for the older compared to the younger adults, indicating a reduction in the efficiency of the attention-related processing required to perform the conjunction serial task with age. The finding of such age-related deficits in study two were in agreement with the results of previous studies by Plude and Doussard-Roosevelt, (1989); Oken, Kishiyama and Kaye, (1994) and Madden, Pierce and Allen, (1996). The conjunction task in study two also revealed significant age-related changes in stimulus processing, response and encoding as measured by the intercept value (the difference in intercept values in study one failed to reach significance). The results of the percentage correct responses in study two failed to indicate any significant age-related decrement, this was also true in study one.

So although the conjunction visual search technique indicated some age-related changes in attention-demanding serial search, whether these changes are significant or not appears to be a product of the number of individuals taking part. The results from both study one and two indicated that there were wide variations in individual performance on this task. It was unfortunate that no more individuals with Alzheimer's disease could be recruited in order to determine whether the comparison of larger groups of older individuals and individuals with AD, still resulted in a greater deficit in AD compared to normal ageing. So although in study one, a greater deficit in conjunction serial search was found in AD compared to normal ageing, further research is required to determine whether this is also the case when larger numbers of people are tested[204].

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[204] The measurement of target absent responses in study two provided a significant age-related effect only in terms of stimulus processing, as measured by the intercept, which was also the case in study one, indicating an age-related reduction in processing efficiency.

4.17 (b) THE SIZE SERIAL SEARCH TASK

As predicted, the target present condition of the size serial search task did require greater recourse to the serial application of visuospatial attention than the conjunction task. There was a significantly greater age-related deficit in intercept value for the size compared to the conjunction task, which indicated that the size task was harder to perform. The target present condition of size task did not however produce the proposed extra age-related decrement in visual search processing in terms of slope value compared to the conjunction task. The target absent condition of the size task did however produce a significant extra age-related decrement in terms of slope value.

The results from study two indicated that whether age-related deficits were found in attention-related visual search appeared to depend upon the characteristics of the search task employed and whether search was for the presence or absence of a target.

The reason why the target present condition of the size task failed to result in greater age-related deficits compared to the conjunction task which appeared to require less attention, was not clear from the present study.

4.18 GENERAL NOTES

The visual search technique was able to reveal changes in visual processing associated with both normal ageing and ageing accompanied by Alzheimer's disease. Although the visual search technique was able to further characterise the effects of AD on early, automatic visual processing, see the discussion of the results (section 4.10) for Study One, the overlap of results between the three groups and between the pop-out and serial search tasks found in the present study would probably preclude the use of such tests as peripheral indicators of the presence of AD, particularly at the individual level.

It may be possible however, with further research to manipulate visual search task parameters in order to create the optimum conditions for obtaining the most sensitive indicators of age and or AD-related change. Numerous other factors such as target distractor combination, task complexity, visual field structure, memory and training, (see Wolfe, 1994 for a review) also appear to influence the result of visual search studies.

Consequently it must be considered when utilising the visual search technique for ageing and AD research that both ageing and AD may interact differently with some of these factors in both automatic and attention-related processing.

CHAPTER FIVE: PUPILLOMETRY

5.1 INTRODUCTION

The pupillary light reflex is a rapid, reflex constriction of the sphincter pupillae muscle of the adjustable diaphragm around the pupil, the iris, in response to light. The pupillary light reflex is mediated by subcortical visual projections, (which extend to the pre-tectal area and the oculomotor nuclei of the mid-brain) and the autonomic nervous system (ANS).

Of particular relevance to the present study is the neural organisation of the reflex. This includes several sites of peripheral and central cholinergic activity. Although evidence for the involvement of peripheral acetylcholine mechanisms in AD is unclear, the central changes in acetylcholine function are well documented. In particular, AD has been associated with the degeneration of the Edinger-Westphal nucleus, a central acetylcholine-related region which sub-serves the pupillary light reflex. One would predict therefore that the resultant disruption in function of this area would result in abnormalities in the kinetics of the pupillary light reflex associated with the central relays in Alzheimer's disease.

To test this prediction the aim of the present study was to measure the kinetics of the pupillary light reflex in both normal ageing and in Alzheimer's disease using the technique of infra-red pupillometry. A further objective was to explore the possibility of whether such measurement could provide a potential peripheral marker for the presence of AD.

The following sections will provide a description of the pupillary light reflex in theoretical and clinical terms and a review of previous research into pupillary function in ageing and in Alzheimer's disease.

5.2 THE PUPILLARY LIGHT REFLEX

Although the physiological significance of the reflex is not entirely clear, the size of the pupil is generally considered to regulate the amount of light entering the eye and thus reaching the retina, (i.e., as light intensity increases the pupil constricts) and to increase the depth of field (Slamovits and Glaser, 1995).

The size of the pupil is determined by the reciprocal actions of the iris muscles. The contraction of the radially oriented dilator pupillae muscle (the fibres of which originate in the outer part of the iris and run radially to insert into the pupillary margin) results in enlargement of the pupillary diameter. The contraction of the circularly oriented constrictor sphincter pupillae (the fibres of which encircle the pupillary border of the iris, forming a sphincter) results in reduction of the diameter of the pupil. The sphincter pupillae muscle is innervated by parasympathetic nerve fibres (although some sympathetics

also terminate in this muscle[205]). The dilator pupillae muscle is innervated by sympathetic nerve fibres[206] (Forrester et al., 1996).

5.3 THE PATHWAYS SUBSERVING THE PUPILLARY LIGHT REFLEX

The pupillary light reflex involves a 6-neuron arc (see figure 5.1, from Forrester, Dick, McMenamin and Lee, 1996). After activation of retinal photoreceptors[207] and a sequential relay through the bipolar cells, the retinal ganglion cells relay luminance information via the afferent axons of the optic nerve. At the optic chiasm, slightly more than one half of the afferent axons in the optic nerve cross to the opposite tract where they are mixed with undecussated axons from the contralateral optic nerve. From the level of the optic chiasm afferent visual and pupillomotor information from either eye is divided into crossed fibres (from nasal retinal receptors of the contralateral eye) and uncrossed fibres (from temporal retinal receptors of the ipsilateral eye). The nerve fibres which serve the light reflex, (the pupillomotor fibres) leave the optic tract in the brachium of the superior colliculus just rostral to the LGN and enter the midbrain synapsing in the pre-tectal nucleus (Adams and Victor, 1993).

From the pre-tectal nucleus the pupillomotor fibres project to the pre-ganglionic Edinger-Westphal (EW) nucleus [208] and (via fibres that cross in the posterior commissure), to the contralateral EW nucleus (Adams and Victor 1993). The EW nucleus is the source of the efferent motor axons which project to the ciliary ganglion from where further neurons project to the sphincter pupillae of the iris (which when innervated, results in pupillary constriction, Slamovits and Glaser, 1995).

The pre-ganglionic fibres running to the ciliary ganglion from the E.W nucleus and the postganglionic fibres from the ciliary ganglion to the neuromuscular junction of the pupilloconstrictor muscle of the iris are cholinergic, i.e., release acetylcholine. There is also evidence from laboratory animal studies that the EW nucleus includes both cholinergic and cholinreceptive neurons (Yum, Wolf and Chiappinelli, 1996; Ichikawa and Shimizu 1998; Juncos, Hirsch, Malessa, Duyckaerts, Hersh and Agid, 1991; Sorenson, Parkinson, Dahl and Chiappinelli (1989).

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[205] Although direct photomechanical activation of the sphincter pupillae muscle fibres has been demonstrated in some mammals (see Gabella, 1991 and Barr, 1989 for reviews also Lau, So, Campbell and Lieberman, 1992), it is generally accepted that in mammals the light reflex and the subsequent pupillary area, is neurally mediated.

[206] With a less apparent parasympathetic innervation.

[207] Both retinal rods and cones furnish afferent impulses for the pupillary light reflex (Lowenstein and Loewenfeld (1959).

[208] (part of the oculomotor or III cranial nerve nucleus, which forms part of the parasympathetic motor pool)

Dilation of the pupil in reduced levels of luminance is mediated by the activation of the peripheral sympathetic innervation of the dilator pupillae via the release of noradrenaline and via central inhibition of the EW nucleus from the posterior hypothalamus (Smith, 1992).

5.4 THE CONSENSUAL PUPILLARY REFLEX

The illumination of one eye results in the constriction of both pupils[209]. This occurs because the fibres sub-serving the light reflex are relayed to both EW nuclei so light falling on either eye excites both nuclei therefore causing constriction of both pupils[210]. The response seen in the illuminated eye is known as the direct response with that in the other eye known as the consensual response.

The consensual light reflex has been used extensively in clinical situations to measure visual system integrity. With complete or nearly complete interruption of the optic nerve, the pupil will fail to react to direct light stimulation; however the pupil of the blind eye will show a consensual reflex, i.e., it will constrict when light is shone in the good eye. The lack of a direct reflex in the blind eye together with lack of a consensual reflex in the sound one means that the afferent limb of the reflex arc is the site of the lesion[211] (Slamovits and Glaser 1995 and Patten 1982). A lack of direct light reflex with retention of the consensual reflex places the lesion in the efferent limb of the reflex arc. In efferent damage, the parasympathetic innervation to the iris sphincter is impaired, and the pupils react poorly to light and may appear to be fixed in the dilated position (Smith 1992)[212].

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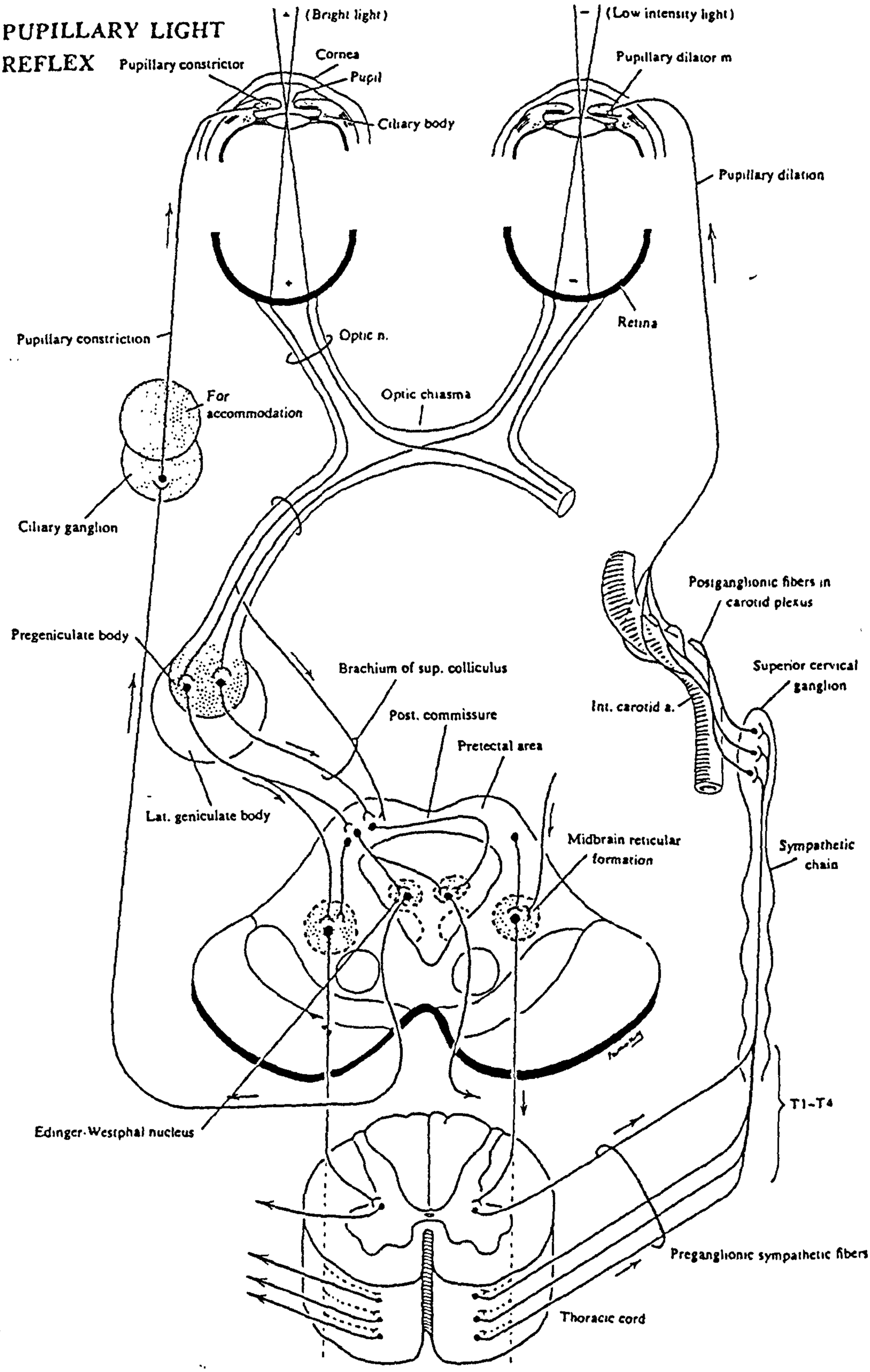
[209] To the same extent (Cox and Parson Drewes (1984).

[210] Such a response is possible because: 1)approximately 80% of the optic fibres from the nasal retinal fields cross the optic chiasm to reach the contralateral pre-tectal nucleus. 2) the right and left pre-tectal nuclei are interconnected by commisural neurons (that pass through the posterior commissure) and therefore a stimulus reaching one nucleus is relayed to the other and 3) each pretectal nucleus sends out fibres to both the right and left EW nucleus (Liebman 1986).

[211] Optic neuritis, glaucoma and optic nerve damage due to multiple sclerosis can cause afferent pupillary defects.

[212] Such effects can be caused by damage to the dorsal midbrain, i.e. the EW nucleus (resulting in the involvement of both pupils), degenerative disease, damage to the iris and damage to the oculomotor nerve (Smith, 1992).

PUPILLARY LIGHT REFLEX



Allen and Budd (1988).

5.5 THE NEAR OR ACCOMMODATION REFLEX OF THE PUPIL

A blurred retinal image or conscious visual fixation on a near object [213] results in accommodation[214,215]. Convergence automatically triggers pupilloconstriction which blocks off the more peripheral rays that strike the cornea and iris, increasing the depth of focus and thus enhancing visual acuity. The light and near effects are additive, i.e., even with the eye brightly illuminated further pupillary constriction is observed when gaze is shifted from distance to near, with the amount of pupillary constriction varying with the nearness of the object of regard (Slamovits and Glaser 1995).

5.6 THE EFFECT OF DIFFERENT VISUAL AND NON-VISUAL FACTORS ON PUPIL SIZE

The pupil can react to changes in factors other than stimulus luminance. For example, the pupil has been found to react to changes in the chromaticity (e.g., Kohn and Clynes, 1969; Young and Alpern, 1980) and in the spatial frequency composition (e.g. Ukai, 1985) of the retinal image[216]. The activity of areas such as the limbic system and hypothalamus[217,218]. also affect pupillary size. There is some

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[213] Although the mode of action of the ciliary muscle is still controversial, it is generally agreed that during accommodation there is some degree of forward and inward shift of the ciliary body which serves to slacken the tension on the suspensory ligament, thus increasing the refractive power of the lens (Forrester, Dick, McMenamin and Lee 1996).

[214] (The alteration of the refractive power of the lens brought about by lens thickening together with the convergence of the eyes and pupilloconstriction).

[215] The neural mechanisms of the accommodation response are poorly understood compared to those for the response to light. It is likely that awareness of decreased object distance evokes accommodative effort originating in frontal centres; while blurred retinal images evoke accommodative effort originating in the occipital cortex. The accommodation reflex therefore involves cortical areas (Slamovits and Glaser 1995). The light and near pupillary reflexes share a common neuronal path only from the EW nucleus onward. Prior to that, the near reflex pathway descends from the occipital cortex, bypassing the pre-tectal nucleus on its way to the EW nucleus. As the fibres approach the nucleus they are situated more ventrolaterally than the light reflex fibres. It is possible therefore to have a spared near response and affected light response with damage to these different areas The final pathway for pupil constriction, whether evoked by light or accommodative effort, consists of the oculomotor nerve, ciliary ganglion and ciliary nerves (Smith 1992).

[216] Barbur and Forsyth (1986) reported that pupillary constriction occurred whenever a uniform stimulus field changed to either a spatially or temporally modulated field of the same mean luminance. This apparent dependence of the pupillary response on the spatial and temporal modulation frequency of the stimulus field requires a geniculostriate input which suggested that the visual cortex could be involved in pupillary responses.

[217] The centre of integration of autonomic function and which is under the influence of the cortex and limbic system (Bannister and mathias, 1992 in Slammovits and Glaser, 1995).

[218] Consequently the emotional and physiological state of the individual also increase pupillary size (via the adrenergic innervation of the dilator pupillae and the inhibition of parasympathetic discharges from

evidence to suggest that the greater the demand on information processing capacities the more the pupil dilates, (Hyona, Tommola and Alaja 1995; Just and Carpenter, 1993)[219]. Pupillary response to light may also be affected by pupil asymmetry (anisocoria) and eye colour, with blue irises tending to have larger pupils than those with brown ones (Alexandridis, 1985 and Adams and Victor, 1993).

Pupillary function may also be changed as a result of systemic illness. For example, larger pupillary diameter after light adaptation, reduced amplitude of contraction and prolonged contraction time at light onset have been associated with Parkinson's disease (Micieli, Tassorelli, Martignoni, Pacchetti, Bruggi, Magri and Nappi, 1991). The pupils of individuals with diabetes have often been described as small with a 'sluggish' reaction to light (Beaumont, Harris, Leendertz and Phillipson, 1987)[220]. Both Adies syndrome[221] and Argyll-Robertson syndrome[222] have been associated with poor or absent pupillary response to changes in luminance (see Smith, 1992 for a review).

Intraocular inflammation causing spasm or atony of the pupillary sphincter, adhesions of the iris from previous inflammation, prior surgical alteration, benign variations from normal, neuropathology due to demyelination, ischaemia, glaucoma, retinal detachment and optic nerve damage, (Slamovits and Glaser 1995 and Alexandridis 1985) can also cause pupillary dysfunction.

It is clear therefore that numerous factors in addition to changes in luminance can affect the dynamics of the pupil when performing research on pupillary function.

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the oculomotor nucleus). Alertness, fright, anxiety, surprise, loud noises and pain (i.e., states of heightened central nervous system (CNS) arousal) also affect pupillary area (Lowenstein and Lowenfeld 1969; Drischel 1957).

[219] The implication is that the pupillary response is only a correlate of cognitive intensity, i.e., the two are not causally linked.

[220] See also Smith et al. (1978).

[221] A benign condition in which there is degeneration of the ciliary ganglia results in accomodative paresis

[222] Caused by disturbance of the EW nucleus, often by syphilis, results in spastically miotic pupils

5.7 PUPILLOMETRY AND AGEING

The size of the healthy pupil at rest is age-dependent, being small in infancy but gradually increasing to a peak diameter in adolescence, after which the pupil size decreases linearly with age[223] (Adams and Victor 1993). The amplitude of the light reflex has been found to decline with increasing age (Tasman and Jaeger 1995). Smith and Smith (1983) suggested however that the pupillary light reflex amplitude was not affected by age directly, but was a consequence of the age-related reduction in resting pupillary area which imposed a mechanical constraint on the potential for further contraction[224].

Reductions in pupillary constriction velocity, maximum diameter, minimum diameter, and dynamic range, together with an increase in the latency of the light reflex have been found to be a general consequence of the effects of normal ageing, (see Borgmann 1972a; 1972b; Clarke, Piesowicz and Spathis, 1989; Smith and Dewhirst, 1986; Beaumont, Harris, Leendertz and Phillipson, 1987; Straub, Thies and Kerp, 1992).

The dilation of the pupil in reduced levels of illumination has also been found to be less pronounced with increasing age[225] (e.g. Birren, Casperson and Botwinick 1950). Beaumont, Harris, Leendertz and Phillipson (1987) found a reduction in dilation velocity with increasing age as did Straub, Thies and Kerp, (1992). Kumnick, (1995) also reported an increase in dilation latency with increasing age, whereas Beaumont et al., (1987) failed to find an increase in dilation latency with age[226].

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[223] Largely because of differences in techniques of measurement, there is only limited agreement between various published studies; but the following pupillary diameters for the light adapted eye are often taken as typical 4.8 mm at age 10 years; 4.0 at age 45 years and 3.4 mm at age 80 years (Bennett and Rabbetts, 1989 in Forester et al,1996).

[224] A larger pupil can support a larger change in area (i.e., constriction) than can a pupil that is smaller to begin with.

[225] Due according to Smith (1992) to changing levels of supranuclear inhibition and decreasing sympathetic tone.

[226] The results from these ageing studies are however difficult to compare because so many different methods have been used to elicit the response. The general 'area' of such research appears to suffer from a lack of consistency of both response elicitation and methods of measurement. Some measurements have been taken after light or dark adaptation; some have involved a flash of light and others a prolonged continuation of the bright light over a period of seconds.

5.8 PUPILLOMETRY AND ALZHEIMER'S DISEASE

Previous research into the effects of Alzheimer's disease on pupillary function has focused on the effects of the topical application of cholinergic agonists and antagonists.

As the neuromuscular junction of the pupilloconstrictor muscle of the iris is cholinergic in nature anticholinergic drugs such as tropicamide, can block parasympathetic activity[227] by competing with acetylcholine at the effector cells of the iris sphincter. Such action prevents the constriction of the pupil, resulting instead in its dilation (mydriasis) [228]. Cholinergic drugs such as pilocarpine[229], are able to depolarise the effector cells of the muscle and therefore cause miosis (constriction)[230].

Because Alzheimer's disease has been associated with reduced levels of acetylcholine, and because the peripheral neuromuscular junction of the iris is cholinergic nature, Scinto et al. (1994) proposed that the topical application of tropicamide would result in a hypersensitive dilation response of the pupil in Alzheimer's disease compared to that found in normal ageing[231,232]. Scinto et al. (1994) assumed

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[227] Tropicamide is a parasympathetic antagonist.

[228] Some anti-Parkinson disease drugs such as procyclidine, can produce anticholinergic side effects resulting in mydriasis (Alexandridis 1985; Smith, 1992).

[229] A cholinergic agonist.

[230] Mydriasis can also occur after the use of tricyclic anti-depressants and the tranquilliser chlorpromazine has been found to cause both miosis and mydriasis in individuals who have been taking it for several years. Arteriolar vasodilator agents used to treat hypertension can also dilate the pupil via alpha-adrenoreceptor blockade (Smith 1992). There is also some evidence that dual innervation exists for iris muscles with excitatory and inhibitory input to each; with the consequence that the action of any individual drug may not be entirely predictable (Smith 1992).

[231] The impetus for the use of drug related pupillometry to determine pupillary function in AD stemmed from research into Down's syndrome. Individuals with Down's syndrome who reach middle age invariably develop a condition whose neuropathology appears to be identical to that of AD and in most cases exhibit a related dementia (e.g. Potter, 1991). Individuals with Down's syndrome were found to exhibit hypersensitivity to compounds that act as antagonists of acetylcholine neurotransmission (e.g. Sacks and Smith, 1989; Harris and Goodman, 1968; Berg, Brandon and Kirman, 1959). This hypersensitivity was detected by measuring changes in pupil size in response to these antagonists. In view of the similarity between Alzheimer's disease and Down's syndrome, Scinto, Daffner, Dressler, Ransil, Rentz, Weintraub, Mesulam and Potter (1994) suggested that individuals with AD may also exhibit hypersensitivity to these drugs and suggested that such a response could potentially act as a peripheral marker for AD. Scinto et al. (1994) therefore performed a study to investigate this potential.

[232] Although Scinto et al., (1994) failed to explain the physiological basis for pupillary hypersensitivity to acetylcholine antagonists in AD, their general theory appeared to have been based on the phenomenon of 'up-regulation' (thought to be mediated by an increase in the number and activity of the receptors on the end-organ which occurs in response to an organ being deprived of its innervation and acts to increase its sensitivity to the transmitters normally associated with it). According to Scinto et al. (1994) such up-regulation would result in the pupils of individuals with AD showing super-sensitive constriction to a cholinergic agonist (for example pilocarpine) and supersensitive dilation to an antagonist such as tropicamide compared to healthy older adults as a result of AD-related acetylcholine depletion within the neural organisation underlying pupillary function.

therefore that the cholinergic deficits associated with AD were peripheral, i.e., would involve the neuromuscular junction of the iris. Scinto et al., failed however to cite any evidence supporting the existence of peripheral deficits in acetylcholine function in AD. Indeed currently available published research, although describing the central deficts in acetylcholine in great detail fails to provide evidence for peripheral deficits.

Although based on such an assumption, the results of Scinto et als' (1994) study[233] revealed that in contrast to the healthy older adults, individuals with AD displayed a pronounced, hypersensitive dilation response to tropicamide. These results, according to Scinto et al. (1994), indicated that, with few exceptions, the individuals with a diagnosis of probable AD (and those classified as 'suspect' AD), could be distinguished from the healthy controls on the basis of their hypersensitivity to tropicamide. Scinto et al., suggested therefore that such a test could have the potential for a peripheral marker for the presence of AD.

However subsequent research revealed a lack of reproducibility of the results from Scinto's group and highlighted additional problems associated with such studies.

Subsequent studies by Zerfass, Sattel, Daniel, Besthorn and Förstl (1995); Arai, Terajima, Nakagawa, Higuchi, Mochizuki and Sassaki (1996); Loupe, Newman, Green et al. (1996); Growdon, Graefe, Tennis, Hayden, Schoenfeld and Wray[234] (1997); FitzSimon, Waring, Kokmen , McLaren and Brubaker (1997); Reitner, Baumgartner, Thuile, Dilmmaghani, Ergun, Kaminski, Lukas and Dal Bianco[235] (1997) failed to confirm Scinto et als' (1994) results.

In addition, Treolar, Assin and Macdonald, (1996) repeated Scinto et als' (1994) study with a group of individuals with AD and a group with multi-infarct dementia (MID). They found that although the group with AD reacted almost identically to that in the study by Scinto et al, the reaction of the group with MID was indistinguishable from that of the AD group. Kalman, Kanka, Magloczky, Szoke,

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[233] In Scinto et al's (1994) study, the participants were seated in a "dim" room and after resting pupil diameter (baseline) measurements were recorded for one minute from each eye, a single drop of a very dilute solution of tropicamide was administered to one eye (arbitrarily chosen) and a drop of a control solution (sterile water) to the other eye. Measurements of pupillary diameter were taken from each eye at scheduled times over the course of one hour.

[234] Growdon et al. (1997) suggested that the discrepancy between their study and Scinto's, rested with the control subjects. In both studies there was a 20% to 25% increase in mean pupillary diameter in patients with AD; the difference was in the dilation among control subjects: only a 5% increase in the study by Scinto et al. and 25% in that by Growdon et als'.

[235] According to Reitner, Baumgartner, Thuile, Dilmmaghani, Ergun, Kaminski, Lukas and Dal Bianco (1997), the intra-individual variation in both patient and control groups tends to be extremely high, resulting in its lack of specificity.

Jardanhazy and Janka (1997) also found an increased mydriatic response to tropicamide in AD, but once again this was not specific to AD as it also occurred in vascular dementia.

So, in general, the test for hypersensitivity to tropicamide, appears to be ambiguous and of insufficient specificity to provide useful diagnostic information in AD. This lack of specificity occurred even though all the above mentioned researchers made great efforts to eliminate other factors which could potentially confound the results, such as eye trauma, eye medication, anticholinergic or psychotropic medication, cataract surgery, glaucoma, diabetes (Scinto et al., 1994; FitzSimon et al., 1997), anisocoria, macular degeneration, blindness, poor visual acuity (Growdon et al., 1997) fatigue, anxiety and hyperarousal (Scinto et al., 1994).

Some of the lack of specificity described for the 'tropicamide studies' described above, may also be due to the problems associated with the use of a topically applied drug for these measurements. For example, differences in corneal permeability, which affects bioavailability, the kinetics of the drug in the tear film and blinking rate, (Reitner et al., 1997; FitzSimon et al., 1997), the normal variability of pupillary responses to dilating agents, iris pigmentation[236] (Katz, 1995) and the possibility that the quantity of tropicamide instilled was not always the same. Treolar and McDonald, (1996) also report that absorption of tropicamide is likely to be affected by any conjunctival disorder and also that any changes in light intensity may affect the pupillary response[237].

In view of the assumptions regarding the effects of Alzheimer's disease on peripheral acetylcholine activity, the results of such studies may in fact have reflected changes in acetylcholine function at the neuromuscular junction of the iris which were not specific to Alzheimer's disease and which may also have been secondary to factors other than the up-regulation of cholinergic receptors in the iris [238].

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[236] Lightly pigmented irises often respond more to topically administered agents, (Katz 1995) as dark eyes tend to have a thicker iris stroma reducing access to the smooth muscle and some drugs are absorbed by melanin pigment which therefore reduces bio-availability, Smith (1992), (Growdon et al., 1997, however showed no difference between dark and lightly pigmented eyes on the effect of tropicamide).

[237] Several studies have also measured pupillary function in AD in relation to the cholinergic agonist pilocarpine. For example, Katz, (1995) studied the pupillary response to topically administered pilocarpine in 20 individuals with AD and found hypersensitivity of pupillary miosis (constriction). This induced miosis was more than twice as great in the group with AD than in the control group, appearing therefore to provide evidence for up-regulation of cholinergic receptors within the iris of patients with AD. Pomara and Sitaram (1995) and Idiaquez, Alvarez, Villagra and San Martin (1994) also found supersensitive pupillary miosis to the ocular administration of pilocarpine in individuals with AD compared to controls. The studies measuring hypersensitivity to pilocarpine look promising but further studies are required to determine whether there is specificity to AD.

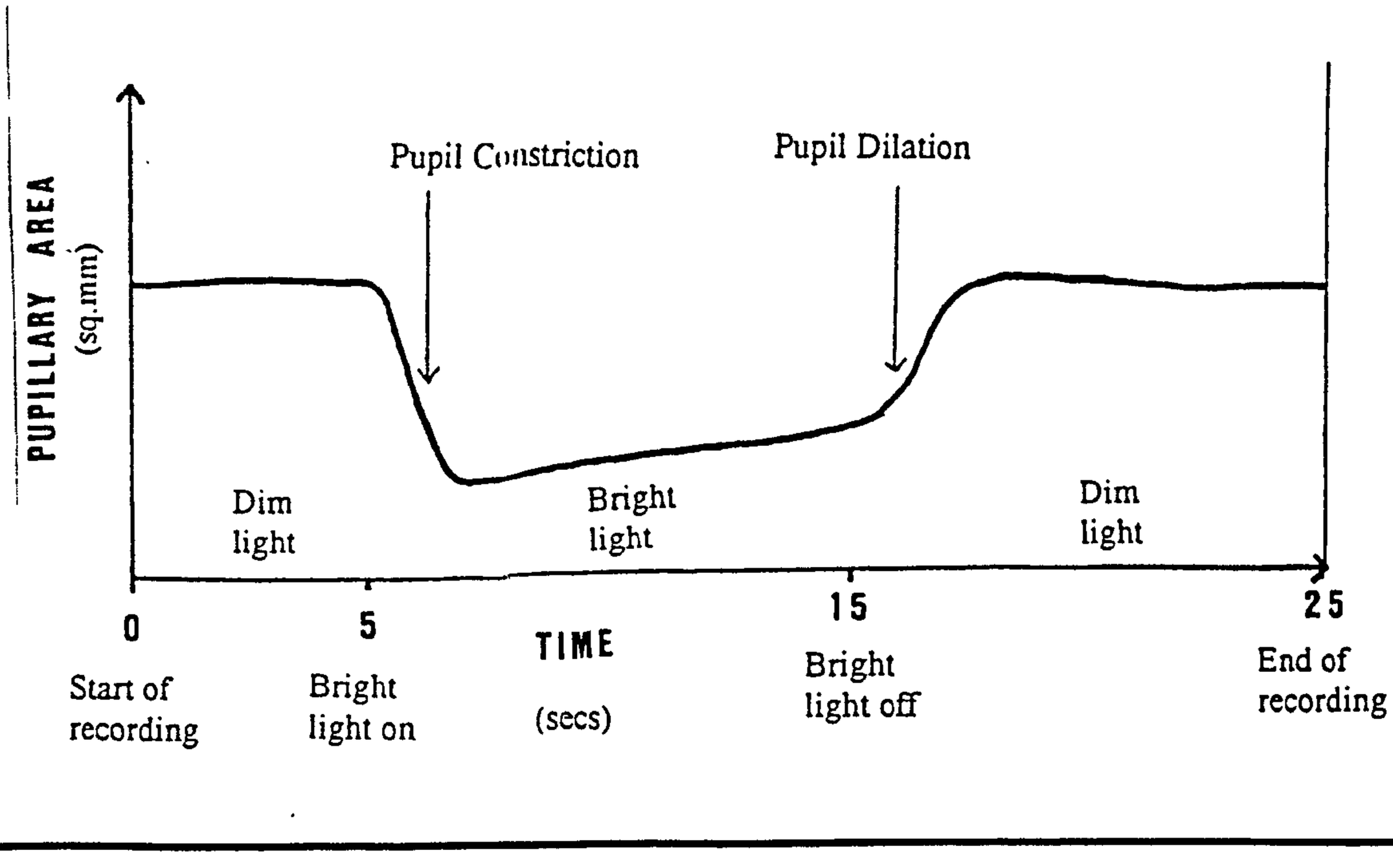
[238] Pomara and Sitaram (1995) also point out an apparent pharmacological anomaly, namely that AD is associated with iris cholinergic receptor supersensitivity to both an antagonist, i.e., tropicamide (Scinto et al 1994) and an agonist, i.e. pilocarpine (Pomara and Sitaram 1995; Katz 1995). Pomara and Sitaram suggest that one would expect to find agonist supersensitivity with antagonist subsensitivity or vice versa and suggest that the most parsimonious explanation is that of a nonspecific corneal epithelial tissue

As the reflex pupillary constriction to bright light reflects both peripheral and central cholinergic relays and as there is evidence for the degeneration in the EW nucleus, (an important central mediator of the reflex and which is both cholinergic and cholinreceptive[239]) in AD, (Hunter, 1985) the measurement of the integrity of the kinetics of the reflex in Alzheimer's disease compared to normal ageing should be better able to reflect changes in cholinergic function associated with Alzheimer's disease.

The aim of the present study was therefore to compare the kinetics of the reflex pupillary constriction to light in Alzheimer's disease compared to normal ageing using the technique of infra-red pupillometry.

Figure 5.2 below illustrates some of the components of this reflex which can be measured.

FIGURE 5.2 STYLISED REPRESENTATION OF THE PUPILLARY LIGHT REFLEX



degeneration that permits abnormal penetration of drugs across the cornea in AD; the reported differences between AD and controls may prove to be a result of non pharmacological factors. Katz (1995) suggests that both studies of cholinergic agonists and antagonists merely illustrate increased corneal penetration of any topical agent in AD patients. Katz (1995) suggests that further pharmacological studies are performed before concluding that up-regulation of cholinergic receptors in the iris allows for recognition of the effects of AD.

[239] Evidence from laboratory animal studies suggest that the EW nucleus includes both cholinergic and cholinreceptive neurons (Yum, Wolf and Chiappinelli, 1996; Ichikawa and Shimizu 1998; Juncos, Hirsch, Malessa, Duyckaerts, Hersh and Agid, 1991; Sorenson, Parkinson, Dahl and Chiappinelli (1989).

The onset of the bright light is associated with, after a certain latency, a rapid pupillary constriction. If the bright light remains on for some time, rather than just a flash, there is some dilation as the eye begins to adapt to the new light level, but when the bright light is turned off, once again after a certain latency, the pupil re-dilates and then continues to re-adjust back towards the original light level.

PREDICTIONS

The present study was designed to test the prediction that reflex pupillary response to the onset of bright light would be abnormal in individuals with Alzheimer's disease when compared to healthy older adults. This abnormality might be expected to manifest itself as:

a) diminished magnitude of constriction

b) increased latency of the response

c) a decrease in the speed of the pupillary constriction.

5.9 EXPERIMENTAL SECTION

5.9 (A) METHOD

(i) PARTICIPANTS

There were three experimental groups, with 12 participants in each. A **young adult group** (5 male, 7 female; age range 22-42 years; mean age 29.5 years; sd 5.6), **an older adult group** (9 male, 3 female; age range 60-81 years; mean age 69.3 years; sd 6, with mini-mental state examination score {MMSE} of above 28 [240] and **a group of individuals with Alzheimer's disease** (4 male, 8 female; age range 57-84 years; mean age 72.16 years; sd 7.3; with a MMSE score of 12-23; mean score 18 : sd 3.1, indicating mild to moderate dementia)[241].

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[240] A normal age-related score on the MMSE

[241] Fifteen older adults were invited to participate and 12 did so, 3 declined; fifteen older adults with AD were asked to participate and 12 did so; 2 declined and one was unable to comply with instructions and the test was abandoned. Informed consent (verbal and written) was obtained for all participants. All participants in the AD group had been diagnosed as having probable Alzheimer's disease in accordance with the diagnosis regime described in chapter one (e.g. NINCDS-ADRDA, McKhann et al 1984 and DSM-IV, American Psychiatric Association, 1994) The older adult group had been diagnosed as not having AD by the same criteria.

(ii) EXCLUSION CRITERIA

Exclusion criteria included; diabetes, other concurrent or past neurological deficits, physical damage to eye or iris, present or previous ocular disease, III nerve palsy, ptosis, cataract and glaucoma. Individuals taking medication such as tranquillisers, antidepressants, neuroleptics, tacrine and neuroleptics or using eye drops (such as artificial tear solutions) were also excluded from entering the study. Exclusion details were determined from the participant (confirmed by the carer in the case of individuals with AD) their medical notes and a clinical examination. All participants had normal or corrected to normal vision[242].

(iii) PARTICIPANT RECRUITMENT

The young adults were recruited from the post-graduate population of the University of Bristol. The older adults were recruited from members of the general public who had taken part in University or memory-clinic research previously and some were the partners of the individuals with AD. The older adults with AD were recruited from the memory clinic patient data base.

(iv) APPARATUS AND TESTING ROOM

The pupillary light reflex was measured by computer analysis of infra-red (IR) images of the pupil. The pupillometer, illustrated in figure 5.3, was head mounted. The stimulating light source (used to elicit the reflex pupillary constriction), the infra-red light source[243] and the infra-red camera and mirror, were attached to the modified frame of a pair of safety goggles. The resultant digitised output from the high quality magnified video image of the pupil enabled computer analysis of the kinetics of the light reflex.

The stimulating light source was a display of 16, high-brightness yellow light emitting diodes[244] (LEDs) situated behind a diffuser, producing a 3cm diameter source of light, positioned in front of and above the eye to be measured. The stimulating light source was positioned about 8cm away from the eye and therefore provided a non-accommodative light source[245].

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[242] Pupillomotor responses are decreased by refractive error that is sufficient to cause a blurring of vision (see Slooter and van Norren, 1980).

[243] The eye is illuminated using IR so that the pupil size would not be affected.

[244] LEDs were used as they produce an instant and linear response in brightness to a change in current, an important factor as the required brightness was ramped gradually to its final level so as not to produce a startle reflex.

[245] To ensure that our results were not confounded by accommodation changes, the light source of the pupillometer which the participants were asked to look at was approximately 8cm away from the eye being tested. This short distance meant that no-one would be able to focus on it so that accommodation should be relatively equal for everyone, i.e., accommodative effort would be the same for everyone as no-one should be able to focus at that distance.

The pupillometer was designed to be lightweight and to measure pupillary light responses in either eye. Being head-mounted meant that should the participant move their head or eyes slightly, the image of the pupil would not be lost. Non-head-mounted pupillometers require the use of chin and head rests in an attempt to keep the participant still. Such a procedure was thought to be inappropriate for use with individuals with AD[246]. The head mounted pupillometer was designed therefore to be easy to put on and take off, be comfortable to wear and to be relatively non-restrictive.

The baseline luminance of the pupillometer light source was 268 cd m^{-2}. During the measurement period this baseline luminance remained at 268 cd m^{-2} for 5 seconds, luminance then increased linearly over 0.5 seconds (to prevent a sudden brightness and startle reflex) to a level of 1400 cd m^{-2} which remained for 9.5 seconds, after which the luminance was 'ramped' down to the original baseline measurement of 268 cd m^{-2} for a further 9.5 seconds after which recording ceased. The total recording time for each run therefore was 25 seconds. The area of the pupil was recorded at a sampling rate of 12.5 Hz and the resolution of the pupil diameter change was approximately 0.02 sq. mm.

The camera focus and the position of the IR glass was adjusted to ensure a clear, focused image of the eye. The pupillometer system incorporated circuitry that recognised the pupil and superimposed a corresponding white disk over this area. Only the responses of the 'white disc' were recorded. This ensured that only change in pupillary area was recorded (i.e., reducing possible artefacts due to extraneous light reflection from other areas of the eye). The eye that was not being tested was occluded from light with a patch.

In view of the potential for clinical application of the pupillary light reflex as a peripheral indicator of the presence of AD the present study was performed in the normal clinical examination room of the memory clinic.

Recordings were made under normal daylight ambient light conditions [247]. Measurement of the ambient light levels within the room was performed over a wide range of daily weather conditions[248]. The

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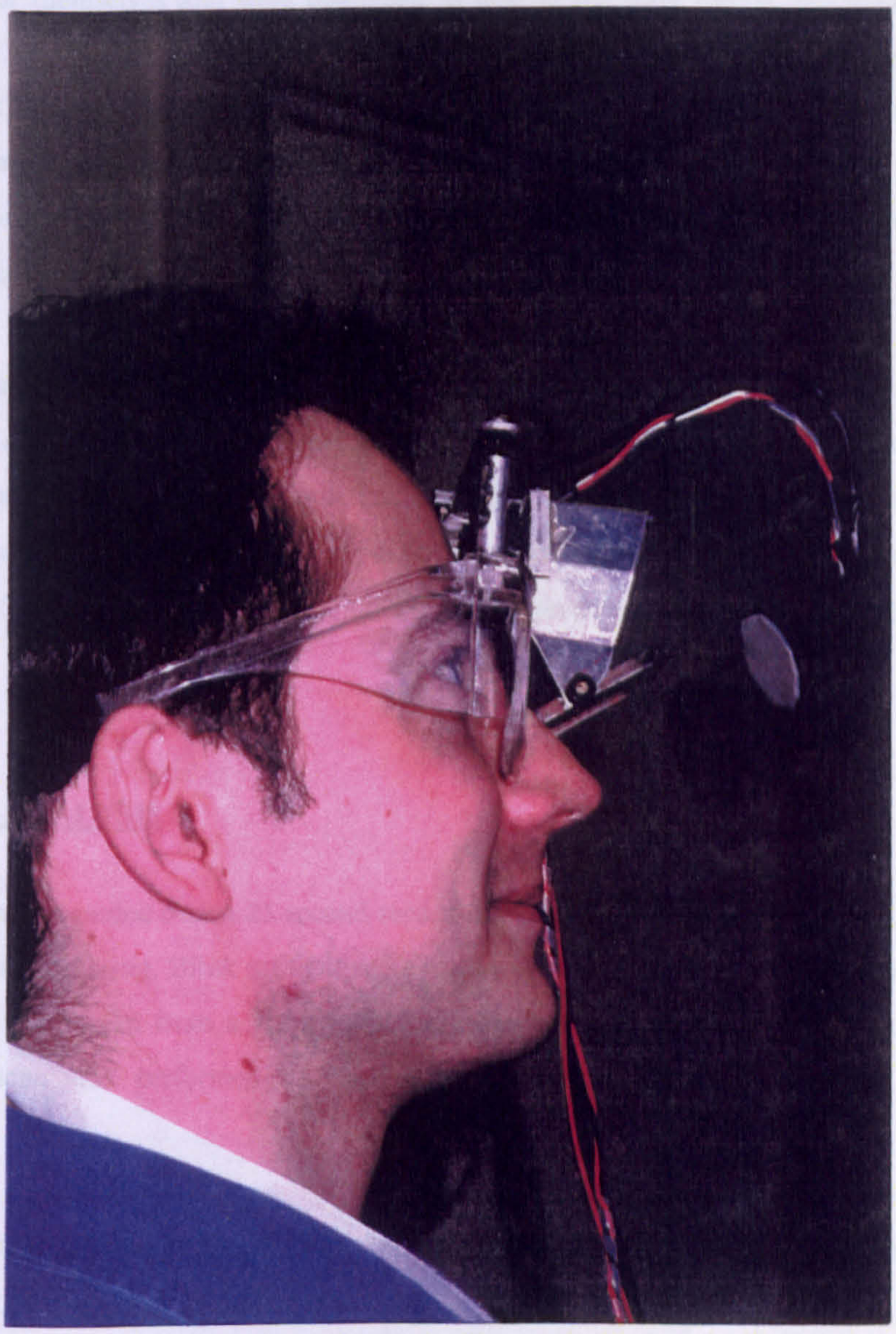
[246] Particularly in terms of discomfort, restriction of movement and the possible feelings of claustrophobia.

[247] Pupillometry is often performed under dark-adapted conditions. The reasons for using daylight conditions in the present study were numerous. It takes approximately 20 minutes to become fully dark adapted, leading to potential difficulties associated with requiring a person with AD to sit in a darkened room. There would have been ethical reservations with this procedure and problems of compliance. Dark adaptation would also lead to a considerable increase in the time spent by the individual with AD in the clinic, particularly when undergoing additional forms of testing. In addition, under normal daylight ambient lighting conditions, the results are not as contaminated by emotion-induced pupillary responses, i.e., psychological influences which are more abundant in darkness where there is a lack of other stimulation. In addition there appears to be no published evidence that within normal ranges, ambient lighting affects the normal pupillary size as this tends to have quite substantial variation in individuals.

ambient light levels ranged from approximately 140 to 250 cdm^{-2} which was below both the luminance of the baseline pupillometer light source (268 cdm^{-2}) and the 'bright' test source (1400 cdm^{-2}). The room was well shielded from extraneous noise. The test was abandoned and then repeated if a sudden noise occurred, to prevent contamination of the data by pupillary dilation to noise or surprise.

[248] The north facing room was never in direct sunlight and the small, highly placed window was always covered by a blind.

FIGURE 5.3 THE HEAD MOUNTED PUPILLOMETER.



(v) PROCEDURE

In an attempt to reduce anxiety and to increase compliance the experimenter demonstrated how the pupillometer was worn and what it measured. The participant was then encouraged to try on the pupillometer for themselves and were instructed to look at the light source, mounted in front of and angled slightly above the eye to be tested. A practice trial was then performed[249]. The participant sat facing a blank, cream-painted wall. A black patch was placed over the eye not being tested. The participants were instructed that three measurements would be taken for each eye, with a break in between each one. They were also asked not to speak, move or blink throughout the procedure until the experimenter had told them that each recording was over[250].

Upon successful completion of the test run, data collection trials began. The procedure was repeated three times for each eye tested[251]. After each run, the procedure was explained again to ensure that the individuals (particularly those with AD) had not forgotten what to do. A break was given between each recording period; the pupillometer was kept in position and before each test procedure the eye was seen to be stable before recording started. The complete test procedure took approximately 15 minutes to perform.

5.9 (B) DATA ANALYSIS

Pupillary area was recorded over a 25 second recording period at a sampling rate of 12.5 Hz and stored on disk for later processing. Blink artifacts were removed at the data analysis stage by extrapolating a straight line in the record from a point just before the blink to a point just after it. This eye-blink removal technique was performed on each individual pupillometry trace before averaging was performed.

The pupillary light reflex was elicited and measured three time for each eye. Computer software was employed to produce a graph of the average response for each individual for each eye. Group averages for the AD, the older adult and the younger adult groups were then determined. Figures 5.4 and 5.5

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[249] The practice run enabled the participant to get used to the testing procedure and provided an opportunity for the experimenter to determine the participant's understanding of the test requirements. That the pupillometer was working correctly and indeed that a pupillary response to light was present for each individual was also made possible by the operation of a practice run.

[250] To reduce pupillary artifacts due to movement or increased ANS activity.

[251] An early version of the equipment enabled only the measurement of the right eye. A later modification permitted the sequential measurement of both eyes. Consequently the right eye was tested in all participants and both eyes were tested in 6 out of the 12 participants in each group.

illustrate the mean pupillary response for these groups (for the right eye only) over the recording period of 25 seconds.

5.10 RESULTS

The availability of the quantified time course of the response enabled it to be parsed into different epochs, see figure 5.5, each of which was then compared across the three groups. The following analyses were performed on the data for the right eye only. The mean pupillary area[252] for the AD, older adult and young adult groups for each epoch are illustrated in table 5.1. These results are presented graphically in figures 5.4 and 5.5.

TABLE 5.1

	GROUP MEAN PUPILLARY AREA (mm^2)		
EPOCH AND TIME PERIOD (in seconds after the start of recording).	ALZHEIMER'S DISEASE	OLDER ADULTS	YOUNGER ADULTS
EPOCH (A) 1 to 4 secs	10.33 sd=6.01	9.7 sd=3.6	13.18 sd=4.3
EPOCH (1) 4 to 5 secs	10.4 sd=6.23	10.03 sd=3.97	13.57 sd=4.55
EPOCH (2) 6 to 7 secs	8.41 sd=6.7	6.83 sd=2.7	8.97 sd=3.3
EPOCH (3) 14 to 15 secs	9.17 sd=6.5	8.24 sd=3.5	11.63 sd=4.3
EPOCH (4) 16 to 17 secs	10.03 sd=6.17	9.72 sd=3.73	13.65 sd=4.6
EPOCH (B) 21 to 24 secs	10.03 sd=5.98	10.1 sd=5.04	14.03 sd=4.97

[252] The raw data for this analysis can be found in table A5.1 of the appendix.

FIGURE 5.4

THE MEAN PUPILLARY RESPONSE FOR THE YOUNG ADULT GROUP, THE OLDER ADULT GROUP AND THE ALZHEIMER'S DISEASE (AD) GROUP : (12 participants in each group: Right eye only measured).

Y = Young adult group

O = Older adult group

AD = Alzheimer's disease group

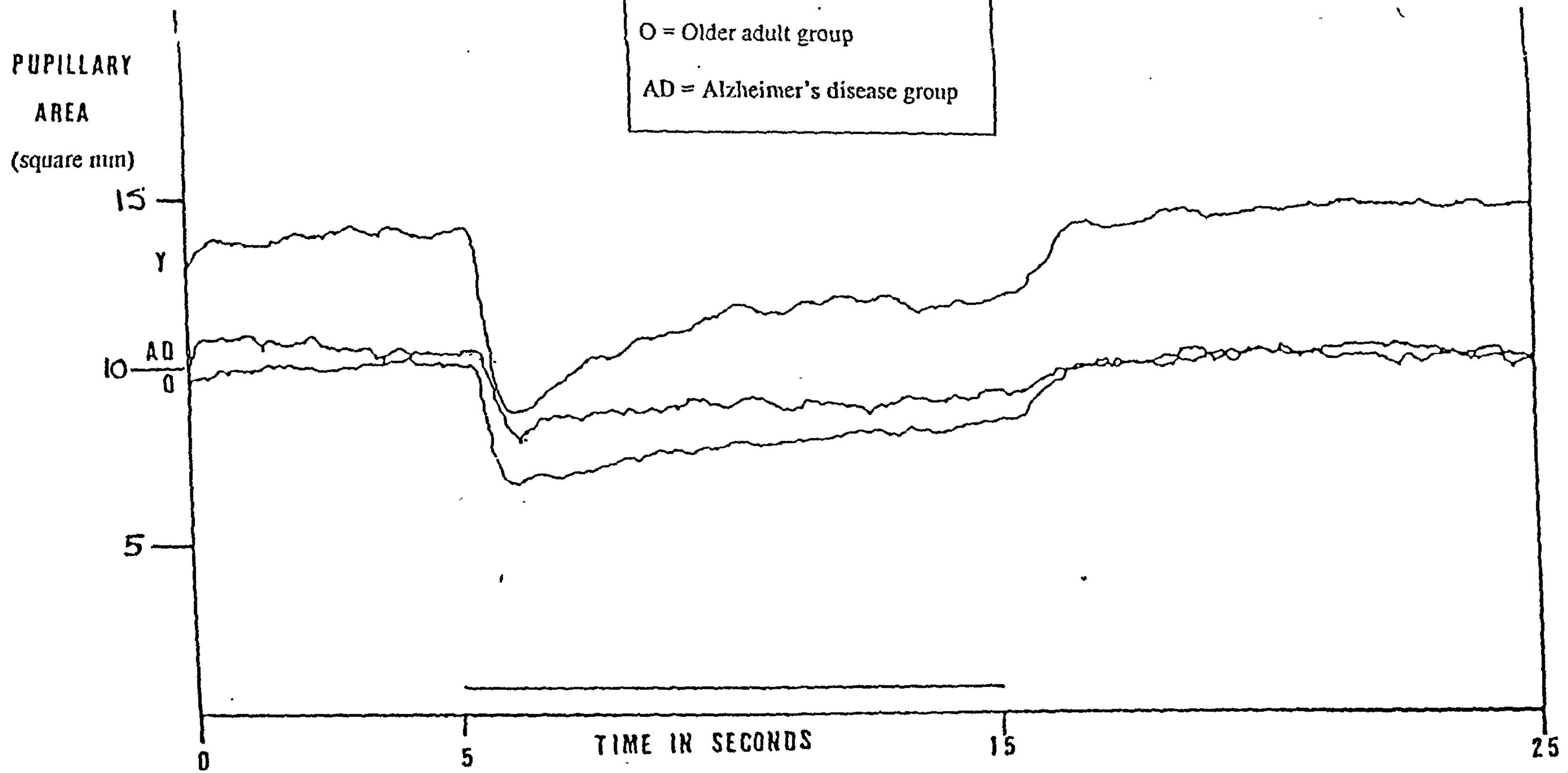

FIGURE 5.5

THE MEAN PUPILLARY RESPONSE FOR THE YOUNG ADULT, OLDER ADULT AND ALZHEIMER'S DISEASE (AD) GROUPS: (12 participants in each group: Right eye only tested).

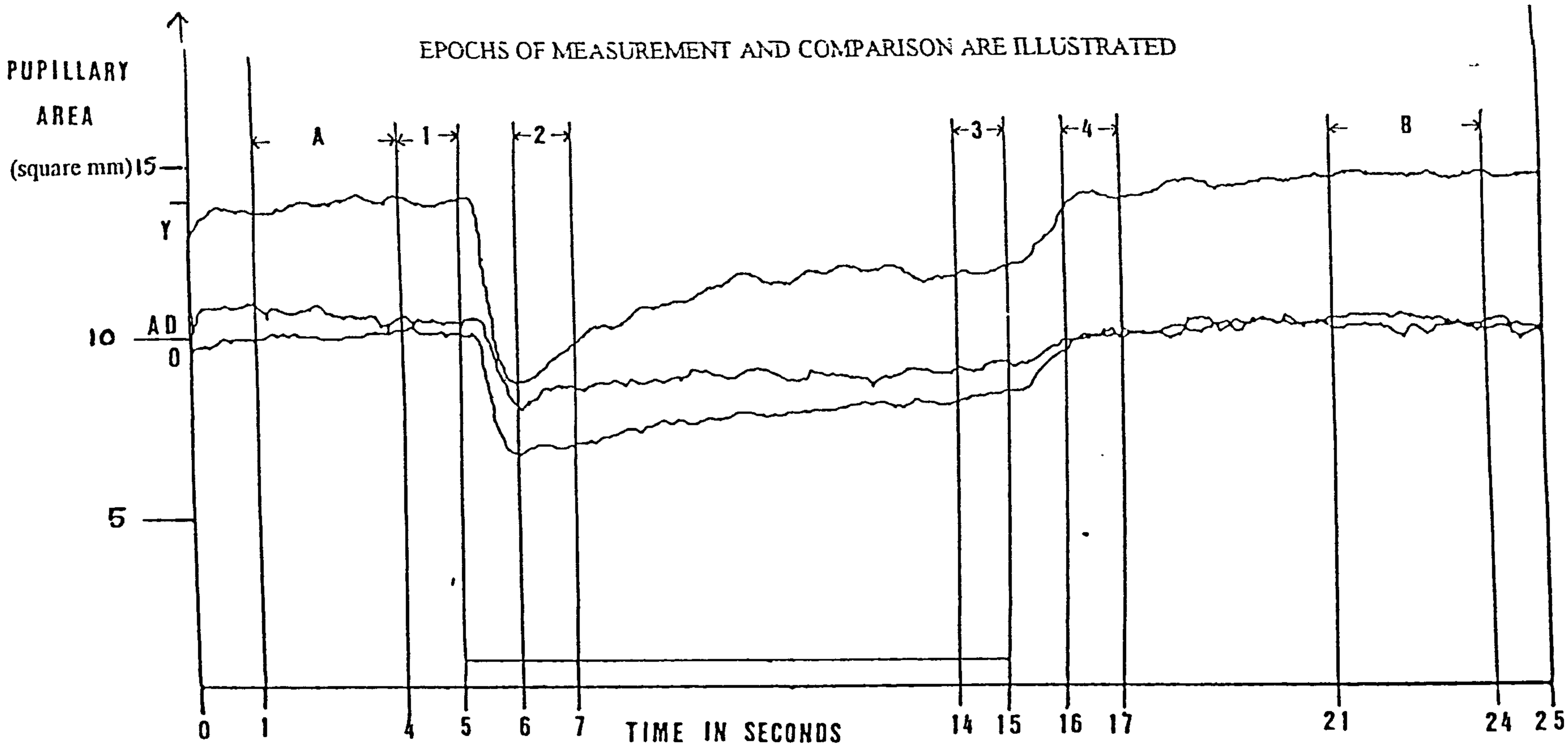

Figure 5.4 Illustrates the mean pupillary area over the 25 second recording period for all three groups. During the baseline period (the first 5 seconds of recording, with the luminance level of 268 cd m^{-2}) the young adult group had the greatest pupillary area compared to both the older and younger adults. This indicated that the pupils of the younger group had a greater baseline or resting pupillary area (i.e. were more dilated at rest) than those of the older and AD group. The finding of a smaller resting pupillary area for old compared to young adults agrees with the findings of previous research (e.g. Straub et al., 1992). The pupillary area of the AD group over the baseline period was however greater than that of the older group.

In response to the increase in brightness which began five seconds after the start of recording, (increasing over a 0.5 second period from 268 to 1400 cd m^{-2}) the pupillary area for all three groups of participants decreased. Pupillary constriction to the onset of a bright light therefore occurred for all three groups. The amplitude of constriction (the difference between the resting pupillary area and the pupillary area at the point of maximum constriction) was greater for the young compared to the older adults. The amplitude of constriction was greater in the old adults compared to those with Alzheimer's disease. Both ageing and Alzheimer's therefore appeared to result in a reduction in the amplitude of the reflex pupillary constriction to bright light, with a greater deficit in the AD group.

This relatively rapid constriction phase (best seen between the 5 and 6 second indicator bars on figure 5.5) was followed by a gradual increase in pupillary area (representing the dilation of the pupil) for all three groups. This dilation during the bright light period (i.e.,1400 cd m^{-2}) presumably indicated the pupillary systems' re-adjustment to the new light level. There was a greater rate of dilation (indicated by the difference in values between epoch two and three, see figure 5.5) for the younger compared to the older group (a result comparable to that found in previous research by Beaumont et al., (1987) and a greater rate of re-dilation change for the old compared to the AD group.

From the point of maximum constriction this gradual pupillary dilation occurred until the brightness of the light source was decreased[253], at the 15 second time point, to its original value of 268 cd m^{-2} when a more rapid dilation occurred for all three groups. Dilation continued until the pupillary area resembled its initial baseline resting level for each group.

Analysis of variance and t-tests were applied to the data to determine whether the differences between the groups reached statistical significance.

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[253] (gradually over a period of 0.5 seconds)

5.10 (a) EPOCH (A); BASELINE PUPILLARY AREA

Epoch (A), a time period of 4 seconds, was used to provide a stable indicator of the baseline or resting pupillary area during the initial period of recording when the pupil was illuminated with and adjusted to, dim light (268 cd m^{-2}). The results of an 1-factor (3-level) independent measures analysis of variance (ANOVA) revealed that the differences in the baseline pupillary area between the groups failed to reach significance, F (df 2,33) =1.67, p >0.05.

5.10 (b) THE PUPILLARY AREA AT EPOCH ONE AND TWO AND THE AMPLITUDE OF PUPILLARY CONSTRICTION.

The measurement of epoch 1 enabled a direct comparison of the pupillary area during a 1-second period of time before the onset of the bright light to that during a 1-second period of time after the onset of the bright light (epoch 2), thus enabling the amplitude of pupillary constriction to be measured[254].

The results of a 1-factor (3-level) independent measures ANOVA revealed that the differences in the baseline pupillary area between the groups during this 1-second time period failed to reach significance, F (df 2,33) = 1.653, p > 0.05. (A result which supports that obtained for epoch (A), the longer measure of baseline area).

The results of a 1-factor (3-level) independent measures ANOVA also revealed that there was no significant difference in the mean pupil area during epoch 2, the period following constriction, between the three groups, F (df 2,33) = 0.66, p >0.05.

The amplitude of pupillary constriction was determined by measuring the change in pupillary area between epochs one and two. Table 5.2, illustrates the mean pupillary area for each group of participants for epoch one and epoch two, with the mean amplitude of pupillary constriction being the result of subtracting the mean pupillary area at epoch two from that at epoch one[255].

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[254] (Epoch 1 can be seen as a representation of the baseline pupillary area, to which an epoch of equal time, i.e., one second, after the onset of bright light can be compared.

[255] (The raw data for this analysis can be found in table A5.1 of the appendix).

TABLE 5.2

	ALZHEIMER'S DISEASE	OLDER ADULTS	YOUNGER ADULTS
MEAN PUPILLARY AREA (mm^2) of Epoch 1.	10.4	10.03	13.57
MEAN PUPILLARY AREA (mm^2) of Epoch 2.	8.41	6.83	8.97
Change in mean pupillary area, i.e. AMPLITUDE of pupillary constriction = epoch 1 - epoch 2, (mm^2)	1.99	3.2	4.6

Paired t-tests indicated a significant pupillary constriction for all groups in response to the onset of bright light: AD group, $t = 4.11$, $df = 11$, $p < 0.01$; older adult group, $t = 6.21$, $df = 11$, $p < 0.01$; younger adult group, $t = 6.96$, $df = 11$, $p < 0.01$.

The results of an 1-factor (3-level) independent measures ANOVA indicated significant differences in constriction between the groups, F (df 2,33) = 5.466, $p < 0.01$. However further analysis with independent measures t -tests, revealed that the difference in the amplitude of constriction between the AD and older adult groups, failed to reach significance, $t = 1.72$, $df = 22$, $p > 0.05$. The difference in the amplitude of constriction between the older and younger adult groups also failed to reach significance, $t = 1.66$, $df = 22$, $p > 0.05$. (There was however a significant difference between the AD and younger adult groups, $t = -3.19$, $df = 22$, $p < 0.01$, with the younger adult group producing the greatest pupillary constriction).

5.10 (c) THE RELATIVE AMPLITUDE OF PUPILLARY CONSTRICTION TO THE ONSET OF BRIGHT LIGHT

The results of the amplitude of pupillary constriction in the three groups did not however take into account the area of the pupil before constriction occurred. It is possible that pupils which are larger

before the onset of the bright light, have a greater 'mechanical' propensity to constrict as they are further from their mechanical constriction limits than those which are small to start with[256].

It is important therefore to take the starting area of the pupil into account when comparing the amplitude of constriction between groups of individuals. This can be achieved by determining the relative amplitude of pupillary constriction, i.e., how much the pupil area changed (i.e., constricted) in relation to its baseline area.

Table 5.3 Illustrates mean relative pupillary constriction between epoch 1 and 2 for the AD, the older adult and the younger adult groups[257].

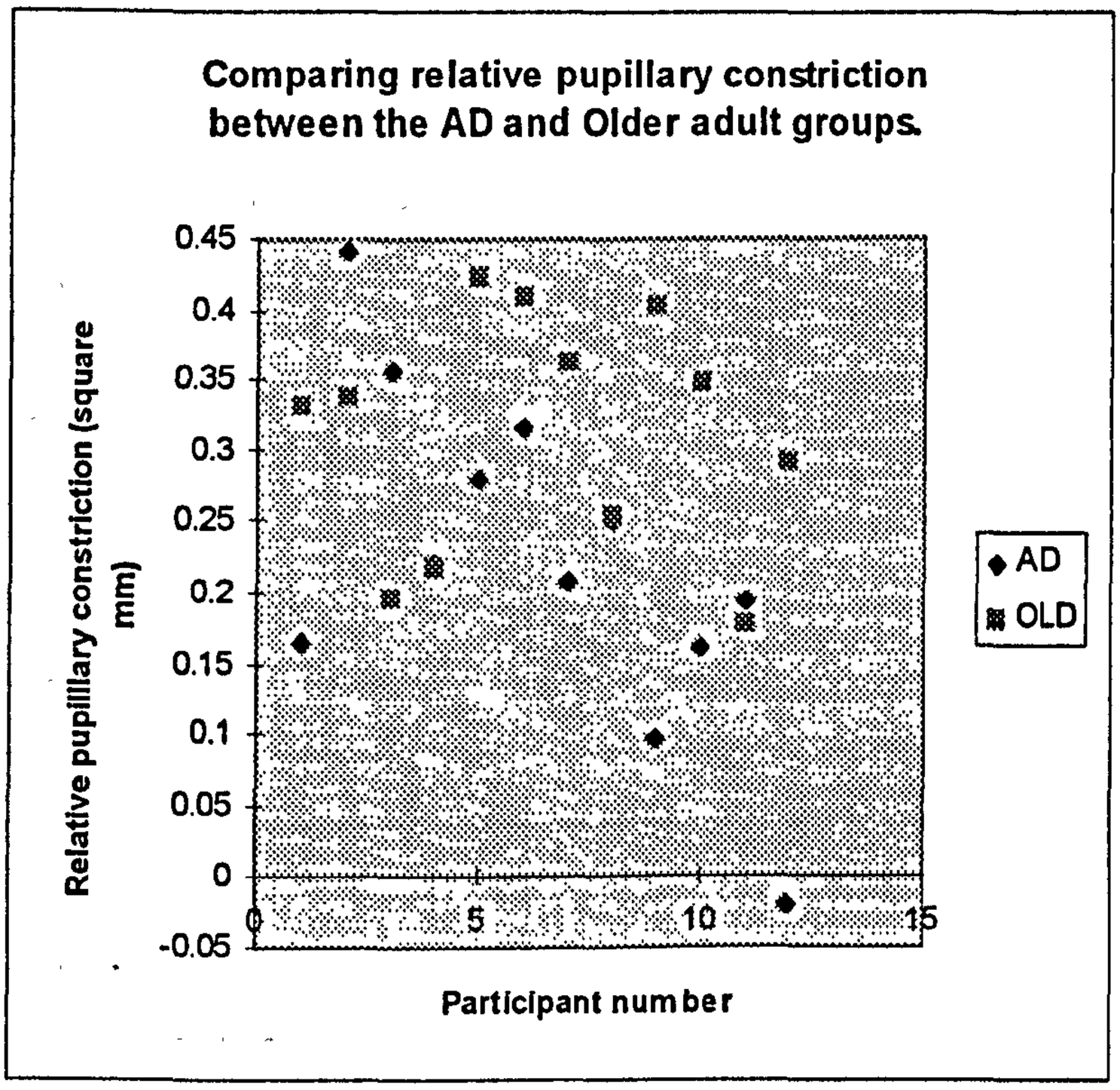
	MEAN RELATIVE RESPONSE AMPLITUDE
AD GROUP	0.2213 sd=0.12
OLDER ADULT GROUP	0.3165 sd=0.08
YOUNGER ADULT GROUP	0.3332 sd=0.087

[256] Individuals with very small pupils (i.e., less than 3.5 mm in diameter) pose a potential problem. When the resting pupillary diameter becomes very small, iris mechanics can interfere with the contraction amplitude of the pupillary response. With very small pupils the amplitude of the pupillary light reflex becomes very small (Kardon, Kirkall and Thompson, 1991). None of the participants in the present study had pupils of this diameter or less.

[257] (Table A5.2 of the appendix illustrates how the relative response amplitudes of the pupillary constriction were determined).

Graph 5.1, provides a comparison of the relative pupillary constriction between the older adult and Alzheimer's disease groups.

GRAPH 5.1



The relative pupillary constriction was greater for the young than for the older adult group, and the AD group had a lower relative constriction value than the older adult group. The results of an 1-factor (3-level) independent measures ANOVA revealed significant differences in relative pupillary constriction between the groups, F (df 2,33) = 4.128, $p < 0.05$.

Further analysis, with independent measures t-tests, revealed that the difference in relative constriction between the older and younger adult groups failed to reach significance, $t = -0.46$, df = 22, $p > 0.05$. The difference in relative constriction between the AD and older adult groups did however reach significance, $t = 2.21$, df = 22, $p < 0.05$, with the greater relative constriction occurring in the older adult group. (Similarly the relative constriction was significantly greater for the young than the AD group, $t = 2.56$, df = 22, $p < 0.02$).

5.10 (d) CORRELATION BETWEEN THE RELATIVE PUPILLARY CONSTRICTION AMPLITUDE AND THE MMSE SCORE IN THE ALZHEIMER'S DISEASE GROUP.

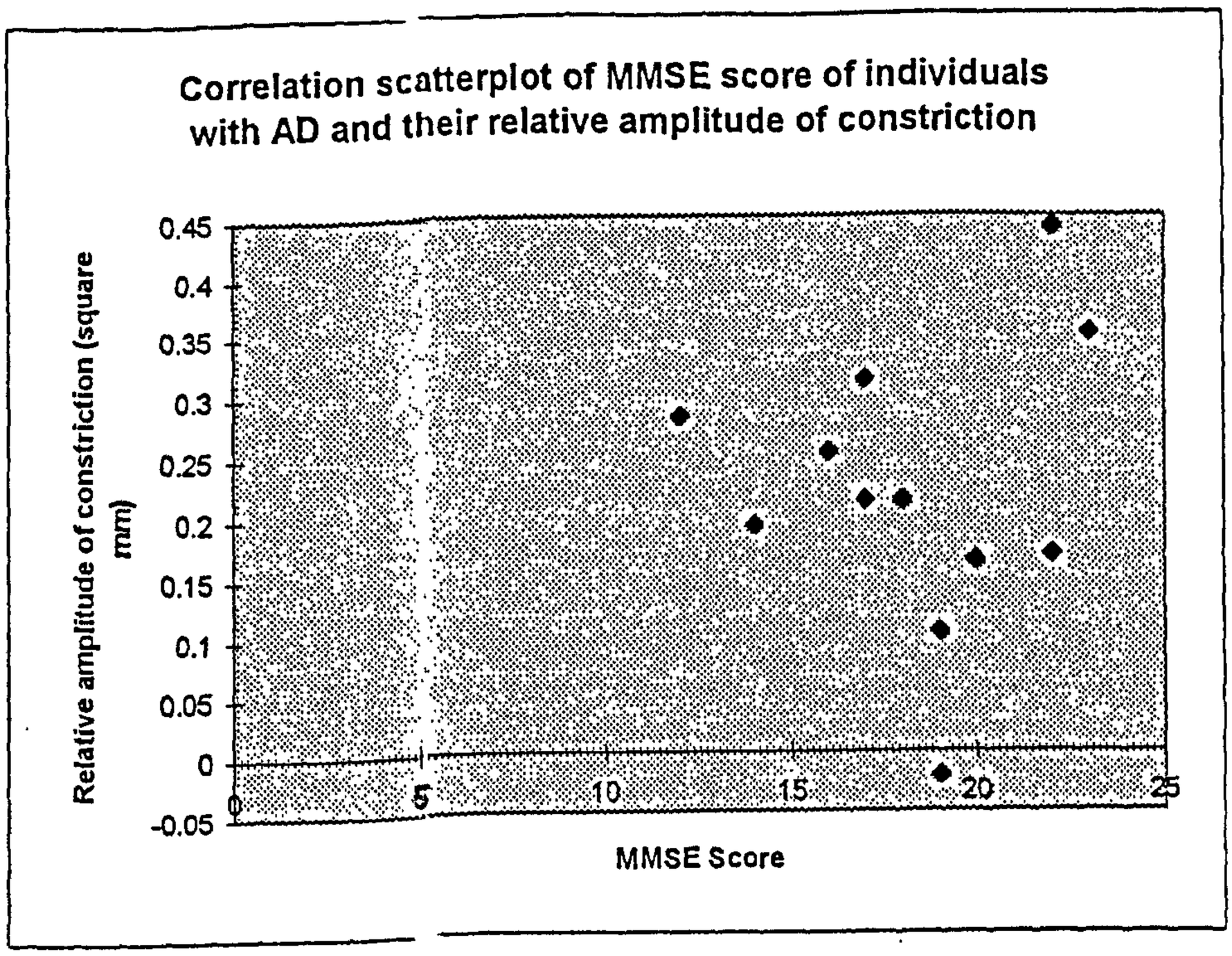
The significantly reduced relative pupillary constriction in AD compared to normal ageing, indicated that pupillary constriction may be sensitive to the effects of AD. Consequently, statistical analysis was performed to determine whether the magnitude of relative pupillary constriction was correlated with dementia severity i.e., the MMSE score (a general measure of the severity of dementia).

TABLE 5.4 Illustrates the relative response amplitude and MMSE score for the individual participants of the AD group.

PARTICIPANT WITH AD	MMSE SCORE	RELATIVE AMPLITUDE OF CONSTRICTION
1	22	0.165
2	22	0.44
3	23	0.35
4	17	0.21
5	12	0.28
6	17	0.31
7	18	0.21
8	16	0.25
9	19	0.1
10	20	0.16
11	14	0.19
12	19	-0.02

A correlation scatter-plot of this data is illustrated by graph 5.1.

GRAPH 5.2 CORRELATION SCATTERPLOT



The results of a Pearson's product moment correlation, indicated that there was no significant correlation between MMSE score and relative pupillary constriction, $r = 0.1$, $df = 10$, $p > 0.05$.

5.10 (e) COMPARING EPOCH 2 AND EPOCH 3: RELATIVE DILATION DURING THE BRIGHT LIGHT PERIOD.

During the bright light period some pupillary dilation occurred for all groups. Table 5.5 Illustrates the difference in mean pupillary areas for epoch 2 and 3 for the AD, older adult and younger adult groups[258].

TABLE 5. 5

	MEAN PUPILLARY AREA (mm^2)		
	AD	OLD	YOUNG
EPOCH 2	8.41	6.83	8.97
EPOCH 3	9.17	8.24	11.63
EPOCH 2 - EPOCH 3	-0.76	- 1.42	- 2.66

The results of paired t -tests indicated that the dilation, (i.e., the increase in pupillary area over this time period) for all groups was significant; AD group, $t = -2.33$, $df = 11$, $p < 0.05$; older adult group, $t = -5.26$, $df = 11$, $p < 0.01$; younger adult group, $t = -5.74$, $df = 11$, $p < 0.01$.

To take into account the initial pupillary area at epoch 2, the mean relative dilation over this time period was determined for the three groups. So, the magnitude of the response was expressed as a proportion of the size of the pupil during epoch 2.

TABLE 5. 6 Illustrates the mean relative dilation for the AD, older and young adult groups[259].

	Mean Relative response amplitude (dilation) between epoch 2 and 3
AD	-0.123 sd= 0.128
OLDER ADULTS	-0.201 sd=0.07
YOUNGER ADULTS	-0.302 sd = 0.13

[258] (The raw data for these results can be found in table A5.1 of the appendix).

[259] The raw data for this table can be found in table A5.3.

There was a greater relative response amplitude for the young than for the old group, and a greater relative response amplitude for the old compared to the AD group.

The results of an 1-factor (3-level) independent measures ANOVA revealed a significant difference in relative re-dilation between the groups F (df 2,33) = 6.6731, $p < 0.01$. Further analysis, employing independent t-tests, revealed however that the difference in relative re-dilation between the AD and older adult groups failed to reach significance, $t = 1.76$, $df = 22$, $p > 0.05$. There was however a significant difference in relative dilation between older adults and younger adults, $t = 2.19$, $df = 22$, $p < 0.05$, (with the younger group having the greater relative dilation) (this was also the case between AD and younger adults, $t = 3.19$, $df = 22$, $p < 0.01$, with the younger adult group having the greater relative dilation).

5.10 (f) THE DILATION RESPONSE TO THE OFFSET OF BRIGHT LIGHT: COMPARING EPOCH (3) TO EPOCH (4).

Table 5. 7 Illustrates the mean pupillary area for the three groups of participants at epoch 3 (the time period 14 to 15 seconds) and at epoch 4 (the time period 16 to 17 seconds)[260]. Epoch 3 represents the mean pupillary area just before the offset of the bright light and epoch 4 represents the mean pupillary area 1 second after the offset of the bright light. The difference in area between epoch 3 and 4 represents the amount of dilation that occurs for each group after the offset of the bright light.

TABLE 5.7

	AD	OLD	YOUNG
EPOCH 3 (mm^2)	9.17	8.24	11.63
EPOCH 4 (mm^2)	10.03	9.72	13.65
difference (3-4) (mm^2)	- 0.85	- 1.48	- 2.02

The results of repeated measures t-tests revealed that for all three groups there was a significant dilation to the offset of the bright light; AD group, $t = -3.05$, $df = 11$, $p < 0.02$; older adult group, $t = -8.14$, $df = 11$, $p < 0.01$; younger adult group, $t = -6.91$, $df = 11$, $p < 0.01$.

To take into account the initial pupillary area at epoch 3, the mean relative pupillary dilation between epoch three and four was determined.

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[260] (The raw data for this section can be found in table A5.1 of the appendix).

5.10 (g) THE RELATIVE DILATION RESPONSE TO THE OFFSET OF BRIGHT LIGHT: COMPARING EPOCH 3 AND EPOCH 4.

Table 5.8 illustrates the mean relative response amplitude for the 3 groups between epoch 3 and 4[261].

TABLE 5. 8

	Mean Relative response amplitude (dilation)
AD	-0.106 sd=0.0096
OLDER ADULTS	-0.197 sd=0.09
YOUNGER ADULTS	-0.182 sd=0.077

The results of an 1-factor (3-level) independent measures ANOVA revealed that the differences in relative dilation failed to reach significance [262] between the three groups, F (df 2,33) = 3.2714, $p > 0.05$.

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[261] The raw data for these results can be found in table A5.4 of the appendix.

[262] (This just failed to reach significance an F value of 3.285 was required for significance)

5.10 (h) COMPARING THE RELATIVE PUPILLARY AREA CHANGE BETWEEN EPOCH (A) AND EPOCH (B).

This analysis was performed to determine the relative extent to which the mean pupillary area of the pupil had returned to its original baseline level after the light reflex.

TABLE 5. 9 Illustrates the mean pupillary area for epoch A and epoch B and the difference between A and B, i.e. the amplitude of any change between the two epochs, for the AD, older and younger adult group[263].

	AD	OLD	YOUNG
EPOCH A (mm^2)	10.33	9.70	13.18
EPOCH B (mm^2)	10.03	10.1	14.03
Difference(A-B) (mm^2)	0.3	- 0.4	- 0.85

TABLE 5.10 Illustrates the mean relative pupillary response amplitude (i.e., taking into account the area of the pupil during epoch A) for the AD, older and younger adult groups[264].

	Mean Relative response amplitude
AD	0.0501 sd=0.128
OLDER ADULTS	-0.0426 sd=0.099
YOUNGER ADULTS	-0.0677 sd=0.139

For both the young and older adult groups, the pupillary area at epoch B was greater than at epoch A, i.e., greater than the baseline level. For the AD group however, the pupillary area at epoch B was smaller than at baseline, i.e., epoch A. , indicating that unlike the young and old groups the AD group had not returned to its original value nor had surpassed it.

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[263] (The raw data for these results can be seen in table A5.1 of the appendix).
[264] The raw data for these results can be seen in table A5.5 of the appendix.

The results of an 1-factor (3-level) independent measures ANOVA indicated that the differences in mean relative change between epoch A and B between all the groups failed to reach significance, F (df 2,33) = 2.7798, $p > 0.05$.

5.10 (i) PUPILLARY CONSTRICTION LATENCY AFTER BRIGHT LIGHT ONSET

The time taken after the onset of the bright light (at 5 seconds after the start of recording), before the pupil starts to constrict is known as the constriction latency. The exact point at which constriction of the pupil began was difficult to determine from the pupillary response graph. Constriction appeared to be gradual rather than sudden, as indicated by the 'shoulder' on the graphs in figure 5.4 and 5.5. In the present study, the latency of constriction was expressed in terms of the time taken from the onset of the bright light (at 5 seconds) to the point where the pupil had constricted to 1/3 [(265)] of its maximum value[266].

Table 5.11, illustrates the mean time taken to reach 1/3 of the maximum amplitude, i.e., the constriction latency for each of the participating groups.[267].

TABLE 5.11

	(A) mean Pupillary area at 5 secs (mm^2)	(B) mean pupillary area at maximum constriction (mm^2)	Amplitude of constriction (A-B) (mm^2)	mean 1/3 amplitude constriction (mm^2)	mean constriction latency, (secs) (time to 1/3 of amplitude)
AD	9.947 sd=6.1	7.41 sd=6.06	2.54 sd=1.77	0.85 sd=0.59	0.6633 sd=0.37
OLDER ADULTS	9.61 sd=3.76	6.31 sd=2.47	3.3 sd=1.63	1.098 sd=0.54	0.485 sd=0.057
YOUNGER ADULTS	13.17 sd=4.4	8.16 sd=2.78	5.01 sd=2.2	1.67 sd=0.74	0.4558 sd=0.039

In response to the onset of bright light, the time delay for the pupils in reaching a third of their maximum constriction was greatest for the AD group. Although the older group were quicker than the

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[265] The value of 'a third of the maximum constriction' was used as this measure fell upon a straight portion of the response curve, avoiding the variability of the later phase of the constriction and the ambiguity of deciding when the response reached a maximum, and also enabled the early part of the response to be assessed.

[266] Other researchers for example Beaumont, Harris, Leendertz and Phillipson ,1987) do not state how latency was measured.

[267] The raw data for this table can be seen in tables A5.6, A5.7, A5.8 of the appendix.

AD group they were slower than the young group. The greatest delay in amplitude in the AD group was not a consequence of the amplitude of the response being greater in AD and therefore taking longer to reach a third of its value, because as illustrated in table 5.11, the greatest amplitude was shown by the young group.

The results of an 1-factor (3-level) independent measures ANOVA revealed however that the differences in latency of constriction between the groups failed to reach significance, $F(2,33) = 3.06$ $p > 0.05$.

5.10 (i) THE SPEED OF CONSTRICTION OF THE PUPIL IN RESPONSE TO BRIGHT LIGHT ONSET.

The speed of pupillary constriction to the onset of bright light was determined by dividing the amplitude of the 1/3 value of constriction (distance) by the time taken to reach this value. These measurements allow us to determine the speed of the response in its early stages. Table 5.12 Illustrates the mean speed over the first 1/3 of the amplitude[268].

TABLE 5.12

	YOUNG	OLD	AD
mean speed of constriction (mm^2/sec) over the first third of the constriction.	3.6853 sd=1.64	2.3059 sd=1.23	1.5417 sd=1.3

The results indicated that the speed of constriction was greatest for the young adults. There was a reduction in speed for the old group compared to the young group and a further reduction in speed in the AD group.

The results of a 1 factor, 3 levels, independent ANOVA indicated that there was a significant difference in speed of constriction between the three groups, F (df 2, 33) = 7.173, $p < 0.01$. Further analysis employing independent measures t tests revealed that the difference in speed of constriction between the young and older adults reached significance, t (df 22) = 2.33, $p < 0.05$ with the younger adults showing the greater speed (a result which agrees with the findings of Beaumont et al., 1987).

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[268] The raw data for these results are presented in table A5.9 of the appendix

The difference between the older adults and AD group however failed to reach significance, t (df 22) = 1.4758, p >0.05. (There was a significant difference in speed of constriction between the young and the AD groups, t (df 22) = 3.546, p < 0.01, with the younger adults have the quickest speed of constriction).

5.11 TESTING BOTH EYES FOR A SUBGROUP OF 6 PARTICIPANTS.

Due to problems in the design of the pupillometer it was not possible to test the pupillary light reflex in both eyes of the initial 6 participants. For the subsequent 6 participants the pupillary light reflex was measured for both eyes. The comparison of the responses between the eyes enabled a check to be made that the results of the present study were not the result of a responses specific to the right eye.

To compare the pupillary response between the right and left eyes only the 6 people from the 12 participant group who had also had their left eyes tested were used in the analysis. The results are shown in figures 5.6 and 5.7.

FIGURE 5.6 ILLUSTRATING THE MEAN PUPILLARY AREA FOR THE RIGHT EYES OF 6 PARTICIPANTS.

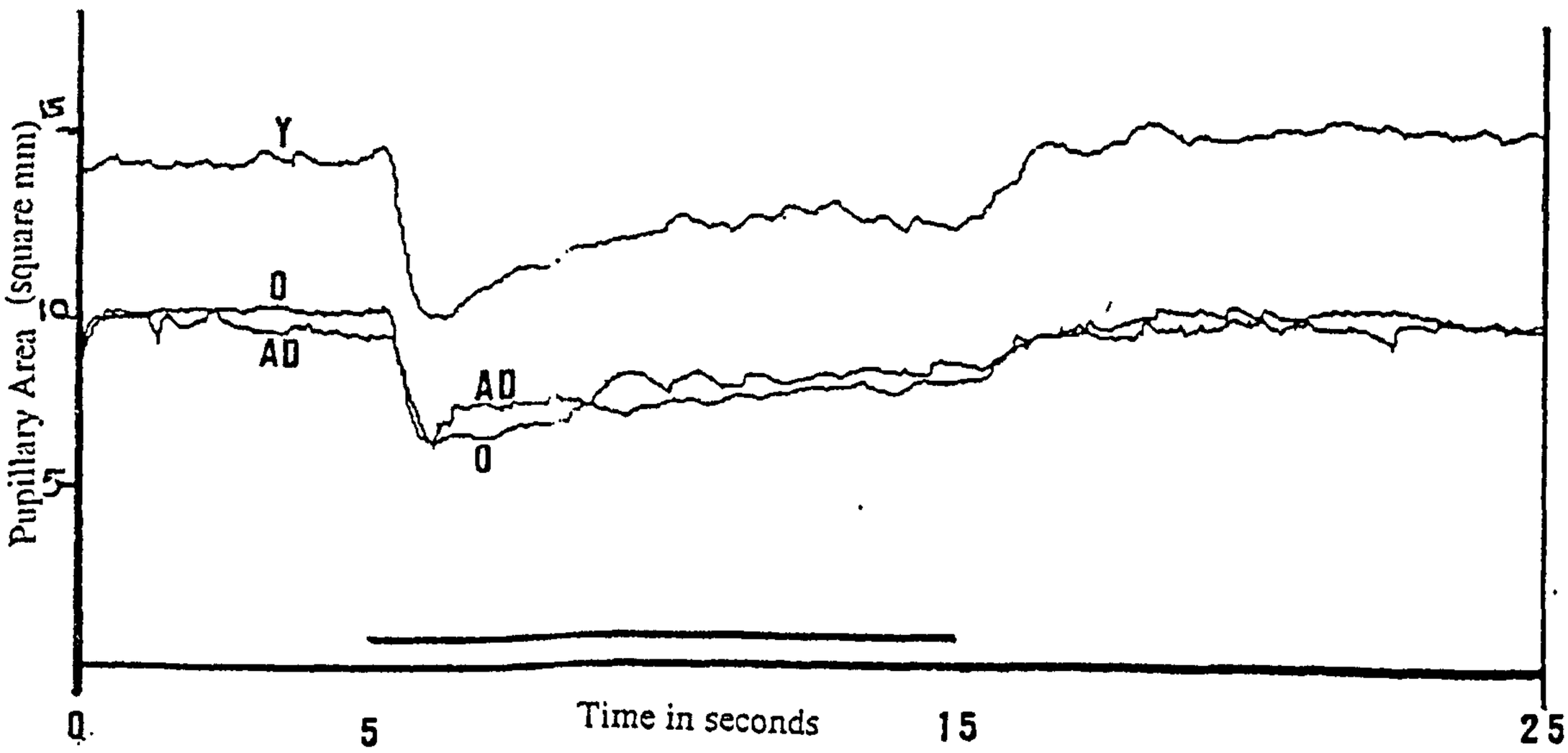
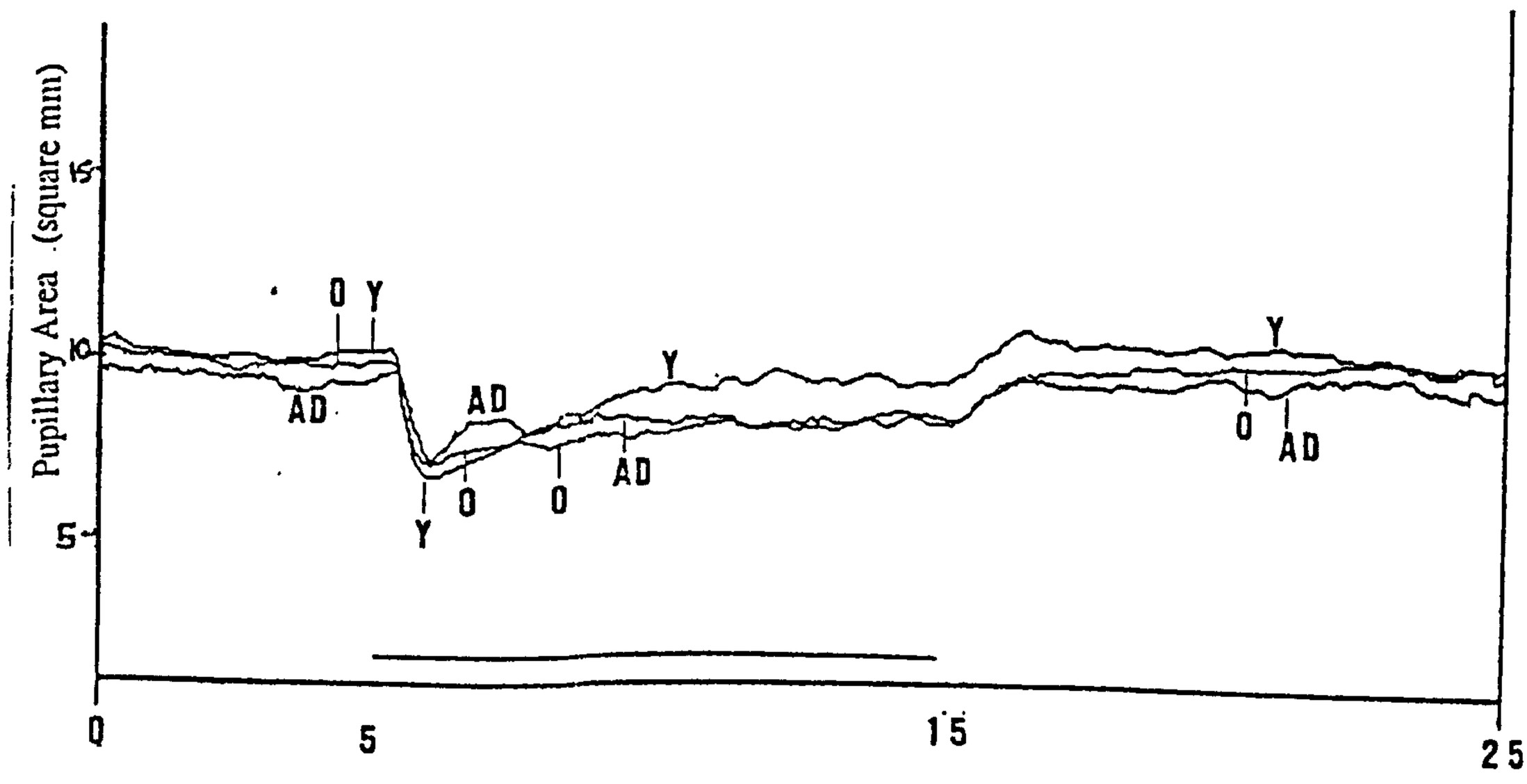


Figure 5.7

The Mean Pupillary Area for the Left Eyes of 6 Participants.



The form of the pupillary light reflex was similar for the right and left eye. Both eyes show a pupillary constriction to bright light and both show re-dilation during the bright light period and a return to near-baseline levels.

Table 5. 13 Illustrates the mean pupillary area for these epochs for the left and right eyes and the differences between them, for the AD, older adult and younger adults[269].

TABLE 5.13

EPOCH	EYE	AD	OLD	YOUNG
1	RIGHT (mm^2)	8.82	9.43	13.48
	LEFT (mm^2)	8.44	9.01	9.31
	DIFFERENCE (R-L) (mm^2)	0.38	0.42	4.17
2	RIGHT (mm^2)	6.62	6.17	9.7
	LEFT (mm^2)	6.97	6.47	6.17
	DIFFERENCE (R-L) (mm^2)	- 0.35	- 0.3	3.53

For epoch 1, the mean pupillary area was greater in the right than in the left eye for all three groups. For both the left and right eye the young group had a larger area than the old group and the old group had a larger area than the AD group. A two-factor split plot (mixed) ANOVA (one between subjects variable and one within subjects variable) analysis revealed that the difference in area at epoch one between the right and left eyes failed to reach significance, F (df 1,6) = 0.7, $P > 0.05$. The difference in pupillary area between the groups also failed to reach significance, F (df 2,20) = 3.039, $p > 0.05$.

For epoch 2, a two-factor split plot (mixed) ANOVA (one between subjects variable and one within subjects variable) analysis revealed no significant difference between the right and left eye F (1,6) = 0.5, $p>0.05$ and no significant difference between the groups, F (df 2,20) = 1.34 , $p>0.05$.

Over the first two epochs the pupillary light reflex was therefore comparable for both eyes.

[269] The raw data for this table can be found in tables A5. 10 and A5.11 of the appendix.

5.12 DISCUSSION OF RESULTS

The results of this study demonstrated that the relatively simple technique of infra-red pupillometry was able to demonstrate changes in pupillary function as a result of both ageing and Alzheimer's disease.

Although all three groups exhibited a significant pupillary constriction to the onset of the bright light, a significant protracted, slow dilation over the bright light period and a significant, rapid phase of dilation to the offset of the bright light, there were differences in specific aspects of this response between the groups.

In comparison to young adults, older adults had a reduced resting or baseline pupillary area, a reduced amplitude of constriction in response to bright light, a reduced relative amplitude of constriction to bright light, a reduced rate of relative re-dilation over the bright light period, a longer constriction latency and a slower speed of initial constriction. These differences between the young and old groups reached significance however only in terms of the relative re-dilation over the bright light period and of the speed of constriction in response to the onset of bright light.

Importantly and as predicted, the relative pupillary constriction to bright light was significantly reduced in AD compared to normal ageing, (see section 5.10 b). The finding of a significant deficit in the efficiency of pupillary constriction[270] relative to its resting stage in AD compared to normal ageing represents an important finding. The reduction in the efficiency of pupillary constriction probably reflects the degeneration of the central relays and the disruption of central cholinergic function involved with the pupillary light reflex. If indeed this is the case then the pupillometry technique used in the present study may have the potential to provide quantitative data on the central cholinergic depletion in AD[271].

Compared to the older adult group the AD group also had a larger baseline pupillary area (but smaller than that for the young adults), a smaller amplitude of constriction to bright light, a smaller relative constriction amplitude, a smaller relative dilation response over the bright light period, a smaller relative dilation response to the offset of bright light, a longer constriction latency and a slower speed of constriction. However, although indicating that the kinetics of the pupillary light reflex in Alzheimer's

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[270] In terms of the significant reduction in the amplitude of constriction and the non-significant reduction in latency and speed of constriction compared to older adults.

[271] The deficits in AD in pupillary dilation compared to normal ageing, although not statistically significant, may also point to other potentially measurable deficits in the ability of the hypothalamus to inhibit the action of the EW nucleus and the efficiency of the sympathetic activation of the iris-dilator muscle.

disease exhibited greater changes than those seen in ageing alone, these differences failed to reach significance.

As it was not possible to carry out these tests in a room with strictly controlled ambient lighting it might be argued that had this been the case, a measure of variance might have been removed which would have increased the levels of significance of the observed effects. Though it has been argued that the ambient illumination probably had little effect because it was less than the foveated light source at baseline, we cannot know how important the factor may have been. However in terms of a potential clinical test, one which was very sensitive to local conditions would have limited utility[272].

The results of the present study indicated that at group-level there was a significant AD-related decrement in pupillary constriction. For diagnostic purposes however there needs to be little or no overlap between the groups. For the pupillary response evoked in the present study this was not the case, as illustrated by graph 5.1. (The raw data for this graph can be found in table A5.2 in the chapter five appendix).

However, the results could be of potential physiological value in terms of further characterising the effects of AD. The potential of the pupillometry technique to provide quantitative data on central cholinergic status may also be of potential use in the measurement of disease progression and the efficacy of drug treatments. For example, as AD tends to be characterised by the progressive depletion of central acetylcholine levels one may expect to find an associated reduction in pupillary constriction amplitude[273]. Also, as much of the research into drug treatments of AD are associated with restoring or stabilising central acetylcholine levels, pupillometry may provide a means of indicating the efficacy of treatment with such drugs over a period of time.

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[272] It might also be argued that a study with larger groups might also have led to more significant differences on the various measures. However, differences which appear only when large groups are studied have very limited uses for diagnostic purposes.

[273] There was no significant correlation in the present study between pupillary constriction amplitude and MMSE score but this result may have been due to the small numbers of participants used and also the narrow range of MMSE scores used.

SYNOPSIS

Changes in the functional integrity of several aspects of visual processing were measured in relation to both normal ageing and ageing associated with Alzheimer's disease. The study focused particularly on the measurement of the automatic visual processing traditionally associated with the striate cortex; an area often quoted as being relatively spared from the pathological affects of Alzheimer's disease.

A visual analogue of the auditory mismatch negativity was developed and tested. The successful elicitation of this electrophysiological component in the visual modality enabled its inclusion in the present study as a novel method for the measurement of automatic visual processing. In a test of the automatic visual stimulus change detection underlying the production of the visual mismatch negativity, individuals with Alzheimer's disease were found to have a pattern of deficits inconsistent with those associated with normal ageing. In particular, the responses to standard or commonly presented stimuli, were much reduced in amplitude compared to the responses found in normal ageing. In comparison, the response to rarely presented or deviant stimuli, was very similar for both the individuals with Alzheimer's disease and those who were ageing normally. Such findings, with further research, may have some potential for use in the diagnosis of Alzheimer's disease.

Further evidence for Alzheimer's disease-related deficits in automatic visual function came from measures of visual search efficiency. Although the performance of automatic target detection (as measured by visual 'pop-out') suffered no statistically significant decrement in Alzheimer's disease compared to normal ageing, there was some evidence that such processing was less efficient in Alzheimer's disease. This was particularly the case when the target was surrounded by a large number of distractors and when target detection became more difficult (i.e., individuals with Alzheimer's disease could not, unlike the older adult group, perform pop-out for a target made up from a conjunction of features).

The deficits in visual processing shown by these two studies indicate that even the very earliest stages of visual processing may be abnormal or inefficient in Alzheimer's disease. If indeed this is the case, then the cause of some of the deficits in later visual processing and indeed in higher -level processing in general, may be due to the degradation of the visual information reaching these processes. Such deficits in processing may affect the way in which an individual is able to interact with the environment. The present study also showed that visual target detection requiring the serial application of attention throughout the visual field was reduced in efficiency in Alzheimer's disease compared to normal ageing. This result confirmed the findings from previous studies.

The results from these two studies also indicated that contrary to the prediction of the present study, Alzheimer's disease was associated with a greater detriment in the automatic visual processing

associated with the striate cortex than ageing alone. Such results are of course at variance with the results from many functional imaging studies of the striate cortex, which have tended to illustrate the functional integrity of this area. It may be the case that the electrophysiological measurement of striate visual function is more sensitive to change than are functional neuroimaging studies.

Finally, the pupillary light reflex was tested. The finding of a significantly reduced 'relative amplitude of constriction' to bright light in Alzheimer's disease compared to normal ageing was interpreted as reflecting the central cholinergic dysfunction associated with AD. Such a finding indicates the potential for measuring central cholinergic status in Alzheimer's disease with a simple, non-invasive test. Although such a measurement may not be specific enough for diagnostic purposes it may be potentially useful in terms of measuring the change in an individuals cholinergic status with disease progression or with treatment.

Several distinct aspects of visual function were therefore found to be abnormal in AD compared to normal ageing.

REFERENCES

Aaltonen, O., Niemi, P., Nyrke, T. and Tuhkanen, J.M. 1987 Event-related brain potentials and the perception of a phonetic continuum. Biological Psychology, 24, 197-207.

Aaltonen, O., Tuomainen, J., Laine, M and Niemi, P. 1993 Cortical differences in tonal versus vowel processing as revealed by an ERP component called mismatch negativity (MMN). Brain and Language, 44, 139-15, 1993.

Abrama, R.A. and Dobkin, R.S. 1994 Inhibition of return: effects of attentional cueing on eye movement latencies. J. of Experimental Psychology: Human perception and performance, 20, 467-477, 1994.

Adams, R.D. and Victor, M. 1989 Principles of Neurology, pp. 923-928. New York: McGraw-Hill, 1989.

Adams, R.D. and Victor, A. 1993 Disorders of ocular movement and pupillary function. Chapter 14, Principles of Neurology, 5th Edition. McGraw-Hill, Inc. New York, 1993.

Aguglia, U., Gambarelli, D., Farnarier, G. and Quattrone, A. 1991 Different susceptibilities of the geniculate and extrageniculate visual pathways to human Creutzfeld-Jacob disease (a combined neurophysiological and neuropathological study. Electroencephalography and clinical neurophysiology, 78, (6), 413-423, 1991.

Aigner, T.G. and Mishkin, M. 1986 cited in Fibiger, 1991.

Aine, C.J. and Harter, M.R. 1984 (a) Event-related potentials to stroop stimuli:color and word processing. In R. Karrer, J.Cohen and P. Teuting (Eds.). Brain and Information: Event related potentials. Annals of the New York Academy of Sciences, 425, pp.154-156.

Aine, C.J. and Harter, M.R. 1984 (b) In R. Karrer, J.Cohen and P. Teuting (Eds.). Brain and Information: Event related potentials. Annals of the New York Academy of Sciences, 425, pp.154-156.

Aine, C.J. and Harter, M.R. 1986 Visual event-related potentials to colored patterns and color names: attention to features and dimension. Electroencephalography and Clinical Neurophysiology, 64, 228-245, 1986.

Aks, D. and Enns, J. 1992 Visual search for direction of shading is influenced by apparent depth. Perception and Psychophysics, 52, 63-74, 1992.

Albright, T.D. 1993 cortical processing of visual motion [review]. Review of oculomotor Research, 5177-5201, 1993.

Aldrich, M.S., Alessi, A.G., Beck, R.W. and Gillman, S. 1987 Cortical blindness: etiology, diagnosis and prognosis. Annals of Neurology, 21, 149-158, 1987.

Alexandridis, E. 1985 The Pupil, Heidelberg:Springer-Verlag, 1985.

Alho, K. 1995 Cerebral generators of mismatch negativity (MMN) and its magnetic counterpart (MMNm) elicited by sound changes. Ear and Hearing, 16, 1, 38-51, 1995.

Alho, K., Sams, M., Paavilainen, P., Reinikainen, K. and Naatanen, R. 1989 Event-related brain potentials reflecting processing of relevant and irrelevant stimuli during selective listening. Psychophysiology, 26, 514-528, 1989.

Alho, K., Saino, N., Sajaniemi, N., Reinikainen, K, and Näätänen, R. 1990 Event-related brain potential of human newborns to pitch change of an acoustic stimulus. Electroencephalography and Clinical Neurophysiology, 77, 151-155, 1990.

Alho, K., Woods, D.L., Algazi, A. and Näätänen, R. 1992 Intermodal selective attention. II. Effects of attentional load on processing of auditory and visual stimuli in central space. Electroencephalography and clinical Neurophysiology, 82, 1992, 356-368.

Alho, K., Woods, D.L., Algazi, A., Knight, R.T. and Naatanen, R. 1994 Lesions of frontal cortex diminish the auditory mismatch negativity. Electroencephalography and Clinical Neurophysiology, 91, 353-362, 1994.

Alho, K., Tervaniemi, M., Huotilainen, M., Lavikainen, J., Tiitinen, H., Illmoniemi, R.J. Knuutila, J. and Naatanen, R. 1996 Processing of complex sounds in the human auditory cortex as revealed by magnetic brain responses. Psychophysiology, 33, 369-375, 1996.

Allen and Budd (1988) in Adams and Victor, 1993.

Allison et al 1979 cited in Gilmore 1995.

Allport, D.A. 1977 On knowing the meaning of words we are unable to report: the effects of visual masking. In S. Dornic (Ed.), Attention and Performance (Vol. 6., pp.505-533). Hillsdale NJ: Lawrence Erlbaum Associates, 1977.
Allport, D.A. 1989 Visual attention. In M.I. Posner (Ed.) Foundations of cognitive science, pp.631-682. Cambridge MA: MIT press.
Allport, D.A. 1993 Attention and control: have we been asking the wrong questions ? A critical review of twenty-five years. In Attention and Performance XIV, ed. D.E. Meyer, S. Kornblum, pp 183-218. Cambridge, MA: MIT Press, 1993.
Aminoff, M.J. and Goodin, D.S. 1994 Visual evoked potentials. J. of Clinical Neurophysiology, 11, (5): 493-499, 1994.
Arai, H., Terajima, M., Nakagawa, T., Higuchi, S., Mochizuki, H. and Sasaki, H. 1996. Pupil dilation assay by tropicamide is modulated by apolipoprotein E4 allele dosage in Alzheimer's disease. Neuroreport, 7, 918-920, 1996
Arguin, Joanette and Cavanagh 1993 cited in Parasuraman et al 1995
Armstrong , R.A., Nocklin, D., Sumi, S.M. and Alvord, E.C. 1990 Neuropathological changes in the visual cortex in Alzheimer's disease. Neuroscience Research Communication, 6, 163-171, 1990.
Arnold, S.E., Hyman, B.T., Flory, J., Damasio, A.R. and van Hoesen, G.W. 1991, cited by J.D. Turner in D. Nicholson (Ed.), Anti-dementia agents, pp. 252-271, Academic Press Ltd. 1994.
Arriagada, P.V., Growdon, J.H., Hedley-Whyte, E.T. and Hyman, B.T. 1992 Neurofibrillary tangles but not senile plaques parallel duration and severity of Alzheimer's disease. Neurology, 42, 631-639, 1992.
Assad, J.A. and Maunsell, J.H.R. 1995 Neuronal correlates of inferred motion in primate posterior parietal cortex. Nature, 373, 518-521, 1995.
Aulanko, R., Hari, R., Lounasmaa, O.V., Naatanen, R., and Sams, M. 1993 Phonetic invariance in the human auditory cortex. Neuroreport, 4, 1356-1358, 1993.

Baddeley 1986 Baddeley, A.D. working Memory. Oxford: Oxford University Press, 1986.
Bajalan, A.A.A., Wright, C.E., Vander Vliet, V.J. 1986 Changes in the human visual evoked potential caused by the anticholinergic agent hyoscine hydrobromide: comparison with results in Alzheimer's disease. J. Neurology, Neurosurgery and Psychiatry, 49, 175-182, 1986.
Balota, D.A. and Ferraro, F.R. 1993 A dissociation of frequency and regulatory effects in pronunciation performance across young adults, older adults and individuals with senile dementia of the Alzheimer's type. J. of Memory and Language, 32, 573-592, 1993.
Barbas, H. and Rempel-Clower, N. 1997 Cortical structure predicts the pattern of corticocortical connections. Cerebral Cortex, Oct/Nov, 7: 635-646; 1047-3211, 1997.
Barbur, J.L. and Forsyth, P.M. 1986 Can the pupil response be used as a measure of the visual input associated with the geniculo-striate pathway ? Clin. Vision Sci. Vol.1, No. 1., 107-111, 1986.
Barbur, J.L. and Thompson, W.D. 1987 cited in Barbur, Harlow and Sahraie, 1992.
Barlow, H.B. 1972 Single units and sensation: a neuron doctrine for perceptual psychology. Perception, 1, 371-394, 1972.
Barr, L. 1989 Photomechanical coupling in the vertebrate sphincter pupillae. Critical Review of neurobiology, 4, 325-366, 1989.
Bashore, T.R. 1990 Age-related changes in mental processing revealed by analysis of event-related brain potentials. In J.W. Rohrbaugh, R. Parasuraman and J.R. Johnson, (Eds.). Event-related brain potentials: basic issues and applications, pp.242-275. Oxford University Press.
Beauchamp, M.S., Cox, R.W. and DeYoe, E.A. 1997 Graded effects of spatial and featural attention on human area MT and associated motion processing areas. J. Neurophysiol. 78; 516-520, 1997.
Beauchamp, M.S. and De Yoe, E.A. 1996 Brain areas for processing motion and their modulation by selective attention. Neuroimaging 3 (supplement): 5245, 1996.
Beaumont, S.M., Harris, J.P., Leendertz, J.A. and Phillipson, O.T. 1987 The pupillary light reflex in mild Parkinson's disease. Clin. Vision Sci., vol 2, 123-129, 1987.
Beckers, G. and Zeki, S. 1995 The consequences on inactivating areas V1 and V5 on visual motion perception. Brain, 118, 49-60, 1995.
Benson, D.f., Cummings, J.L. and Kuhl, D.E. 1981 Dementia: cortical-subcortical. Sbstract, Neurology, 31, 101, 1981.

Benson, D.L.P., Isackson, P.J., Hendry, S.H., and Jonesd, E.G. 1991 differential gene expression for glutamate acid decarboxylase and type II calcium-calmodulin- dependent protein kinase in basal ganglia, thalamus and hypothalamus of the monkey. J. of Neuroscience, 11, 1540-1564, 1991.
Beradi, A. 1994 cited in Greenwood et al 1997.
Berg, L. and Morris, J.C. 1990 Aging and Dementia. In Pearlman and collins 1990 ****ref V3.
Berg, J.M., Brandon, M.W.G., and Kirman, B.H. 1959 Atropine in Mongolism. Lancet, 2, 441-442, 1959.
Berg, L., McKeel, D.W., Muller, J.P., Baty, J., et al., 1993 Neuropathological indexes of Alzheimer's disease in demented and non-demented persons aged 80 years and older. Archives of Neurology, 50 (4), 349-358, 1993.
Berthier,M.L., Leiguarda, R., Starkstein,S.E., Sevlever, G. and Taratuto, A.L. 1991 Alzheimer's disease in a patient with posterior cortical atrophy. J. Neurology, neurosurgery and Psychiatry, 54 (12), 1110-1111, 1991.
Birren,J.E., Casperon, R.C., and Botwinick, J. 1950 Age changes in pupil size. J. of Gerontology, 5, 267-271, 1950.
Blanks, J.C., Hinton, D.R., Sadun, A.A. and Miller, C.A. 1989 Retinal ganglion cell degeneration in Alzheimer's disease. Brain Research, 501, 364—372, 1989.
Blanks, J.C., Torigoe, Y., Hinton, D.R. and Blanks, R.H.I. 1996 retinal pathology in Alzheimer's disease. I. Ganglion cell loss in foveal/parafoveal retina.
Boback, P., Bodis-Wollner, I. And Guillory, S. 1987 The effect of blur and contrast on VEP latency: comparison between check and sinusoidal grating patterns. Electroencephalography and Clinical Neurophysiology, 68, 247-255, 1987.
Bodis-Wollner, I. 1988 Altered spatio-temporal contrast vision in Parkinson's disease: the role of dopamine. In Dopaminergic Mechanisms in Vision,I. Bodis-Wollner and M. Piccolino. Liss, New York, 1988.
Bodis-Wollner, I., Atkin, A., Raab, E. and Wolkstein, M. 1977 Visual association cortex and vision in man: pattern-evoked occipital potentials in a blind boy. Science, 198, 629-631, 1977.
Bodis-Wollner, I., Yahr, M.D., mylin, L.H. and Thornton, J. 1982 Dopaminergic deficiency and delayed visual evoked potentials in humans. Annals of Neurology, 11, 478-483, 1982.
Bodis-Wollner, I, Marx, M.S., Mitra, S., Bobak, P., Mylin, L. and Yahr, M. 1987 Visual dysfunction in Parkinson's disease. Loss in spatiotemporal contrast sensitivity. Brain, 110, 1675-1698, 1987.
Bondareff, W., Harrington, C., Wischik, C.M., Hauser, D.L. and Roth, M. 1994 Immunohistochemical staging of neurofibrillary degeneration in Alzheimer's disease. J. of Neuropathology and Experimental Neurobiology, 53 (2), 158-164, 1994.
Borgmann, H., 1972 a. Cited in Straub, Jeron and Kerp, 1992.
Borgmann, H., 1972 b. Cited in Straub, Jeron and Kerp, 1992.
Born, J., Fehm-Wolfsdorf, G., Lutzenberger, W., Voigt, K.H. and Fehm, H.L. 1986 Vasopressinn and electrophysiological signs of attention in man. Peptides, 7, 189-193, 1986.
Born, J., Brüninger, W., Fehm-Wolfsdorf, G., Voigt, K.H., Pauschinger, P. and Fehm, H.L. 1987 (a) Dose-dependent influences on electrophysiological signs of attention in humans after neuropeptide ACTH 4-10. Experimental Brain Research, 67, 85-92, 1987.
Born, J., Kern, W., Fehm-Wolsdorf, G., and Fehm, H.L. 1987 (b) Cortisol effects on attentional processes in man as indicated by event-related potentials. Psychophysiology, 24, 286-292, 1987.
Böttcher-Gander and Ullsperger 1992 cited in R. Naatanen (Ed.) Attention and Brain Function. Lawrence Erlbaum associates, Hillsdale New Jersey, 1992, pp.102-210.
Bouras, C., Hof, P.r., Giannakopoulas, P., Michel, J.P. and Morrison, J.H. 1994 Regional distribution of neurofibrillary tangles and senile plaques in the cerebral cortex of elderly patients: a quantitative evaluation of a one-year autopsy population from a geriatric hospital. Cerebral Cortex, 4, 138-150, 1994.
Braak, H. and Braak, E. 1986 Changed ratio of projection cells versus local circuit neurons in the human isocortex during aging and Alzheimer's disease. Clinical Neuropathology, 5 (3), p.113.
Braak, H. and Braak, E. 1991 Neuropathological staging in Alzheimer's related changes. Acta Neuropathologia, 82, 239-259, 1991.
Braak, H.and Braak, E. 1992 The human entorrhinal cortes-normal morphology and lamina-specific pathology in various disaeses. Neuroscience research, 15 (1-2), 6-31, 1992.

Braak, H. and Braak, E. 1994 cited in J. Hardy ; Amyloid, the presenilins and Alzheimer's disease. TINS, 29, 154-159, 1997.
Bressler, S.L. 1996 Interareal synchronization in the visual cortex. Behavioral Brain Research, 76(1-2), 37-49, 1996.
Broadbent, D.E. 1958, Perception and Communication. London: Pergamon, 1958.
Broadbent, D.E. 1971 Decision and stress. New York:Academic Press.
Broadbent, D.E. 1982 Task combination and selective intake of information. Acta Psychologica, 50, 253-290, 1982.
Bruce, V., Green, P.R. and Georgeson, M.A. 1997 (Eds). Visual Perception, physiology, psychology and ecology, 3rd. ed.; pp. 43-65. Psychology Press, New York.
Büchel, C. and Friston, K.J. 1997 Modulation of connectivity in visual pathways by attention: cortical interactions evaluated with structural equation modelling and fMRI. Cerebral Cortex, 768-778; 1047-3211, Dec. 1997.
Buck, B.H., Black, S.E., Behrmann, M., Caldwell, C. and Bronskill, M.J. 1997 Spatial- and object-based attentional deficits in Alzheimer's disease. Brain, 120, 1229-1244, 1997.
Burns, A. and Levy, R. 1994 Dementia. Chapman and Hall, London, 1994.
Burns, A., Howard, R. and Pettit, W. 1995 Alzheimer's Disease: a medical companion. Blackwell Science, Oxford, 1995.
Butler, S.R., Georggiou, G.A., Glass, A., Hancox, R.J., Hopper, J.M. and Smith, K.R.H. 1987. Cortical generators of the CI component of the pattern-onset visual evoked potential. Electroencephalography and clinical neurophysiology, 1987, 68: 256-267.
Buzsaki and Gage 1989 cited in Hasselmo and Bower, 1993.

Calvert, J.E., Harris, J.P. and Phillipson, O.T. 1990 Effects of L-Dopa on the tilt aftereffect with differing stimulus contrast and test duration. Clinical Vision Science, 5, 87-93, 1990.
Calvert, J.E., Harris, J.P. and phillipson, O.T. 1992 Probing the visual system of Parkinson's disease and chronic schizophrenic patients on depot neuroleptic using the tilt after effect. Clinical Vision science, 7, 119-127, 1992.
Cammann, R. 1990 Is there a mismatch negativity (MMN) in the visual modality? Behavioral and Brain Sciences, 13, 234-235, 1990.
Campbell, K., Bell, I. and Bastien, C. 1991 Evoked potential measures of inforrmation processing during natural sleep. In R. Broughton and R. Ogilvie ((Eds.), Sleep, Arousal and performance, pp.88—116. Cambridge, MA: Boston.
Campbell, K.B. and Lowick, B.M. 1987 Ethanol and ERPs: the influence of distractor stimuli. Alcohol, 4, 257-263, 1987.
Campbell, K.B., Marois, R. and Arcand, L. 1984 Ethanol and ERPs: the effects of rate of stimulus presentation and task difficuluty. Annals of the New York acadamy of sciences, 425, 551-555, 1984.
Campion, Latto and Smith 1983 cited in Shallice 1991
Casagrande, V.A. and Lachhica, E.A. 1992 What are the cytochrome oxidase (co) blobs and interblobs really segregating ? Investigative Ophthalmology and Visual Science, 33 (4), p.900.
Cave, K.R. and Wolfe, J.M. 1990 Modelling the role of parallel processing in visual search. Cognitive Psychology, 22, 225-271, 1990.
Celesia and Daly 1977 cited in Gilmore 1995.
Celesia, G.G., Polycyn, R.D., Holden, J.E., Nickles, R.J., Gatley, J.S., Koeppe, R.A. 1982 Visual evoked potentials and positron emission tomographic mapping of regional cerebral blood flow and cerebral metabolism: can the neuronal potential generators be visualized ? Electroencephalography and Clinical Neurophysiology, 54, 243-256, 1982.
Celesia, G.G., Bushnell, D., Toleikis, S.C. and Brigell, M.G.1991 Cortical bliondness and residual vision; is the second visual sysytem in humans capable of more than rudimentary visual perception ? Neurology, 41 (6), p. 952, 1991.
Celesia, G.G. and De Marco Jr. P.J. 1994 Anatomy and physiology of the visual system. J. of Clinical Neurophysiology 11; 5; 482-492, 1994.
Cheng, K., Hasegawa, T., Saleem, K.S and Tanaka, K. 1994 Comparison of neuronal seloectivity for stimulus speed, length and contrast in the prestriate visual cortical areas V4 and MT of the macaque monkey. J. of Neurophysiology, 71, 2269-2280, 1994.

Cheour-Luhtanen, M., Alho, K., Kujala, T., Saino, K., Reinikainen, K., Renlund, M., Aaltonen, O., Eerola, O. and Naatanen, R. 1995 Mismatch negativity indicates vowel discrimination in newborns. Hearing research, 82, 53-58, 1995.
Chertkow, H. and Bub, D. 1994 Functional activation and cognition: the ^{15}O PET subtraction method, chapter 6, in Kertsez 1994.
Chiappa, K.H. 1989 Evoked Potentials in Clinical Medicine, 2nd Ed., edited by K.H Chiappa. Raven Press, Ltd., New York, 1989.
Ciganek, L. 1961 The EEG response (evoked potential) to light stimulus in man. Electroencephalography and Clinical Neurophysiology, 13, 163-172, 1961.
Clarke, C.F., Piesowicz, A.T. and Spathis, G.S. 1989 Pupillary size in children and adolescents with type 1 diabetes. Diabetic Medicine, 6, 780-783, 1989.
Clark, V.P., Parasuraman, R., Keil, K., Kulansky, R., Fannon, S.., Maisog, J.M., Ungerleider, L.G. and Haxby, J.V. 1997 Selective attention to face identity and colour studied with fMRI. Human Brain mapping, 5, 293-197, 1997.
Coben, L.A., Danziger, W.L. and Hughes, C.P. 1983 Visual evoked potentials in mild senile dementia of Alzheimer type. Electrophysiology and clinical Neurophysiology, 55: 121-130, 1983.
Coburn, K.L., Ashford, J.W. and Moreno, M.A. 1991 Visual evoked potentials in dementia: selective delay of flash P2 in probable Alzheimer's disease. The J. of Neuropsychiatry and Clinical Neurosciences 3: 431-435, 1991.
Coburn, K.L., Ashford, J.W. and Moreno, M.A. 1993 Delayed late component of visual global field power in probable Alzheimer's disease. J. of Geriatric Psychiatry and Neurology Vol. 6, 72-77, 1993.
Cogan, D.G. 1979 Visuospatial dysgnosia. American J. of Ophthalmology, 88, 361-368, 1979.
Cohen, J., Cronin-Golomb, A., Growdon, J.H. and Corkin, S. 1988 Color vision deficits in Alzheimer's disease. Society for Neuroscience Abstracts, 14, 219, 1988.
Colby 1991 The neuroanatomy and neurophysiology of attention. J. Child Neurology. 6, S90-S118, 1991.
Connelly, S.L. and Hasher, L. 1993 aging and the inhibition of spatial location. J. of experimental Psychology: Human perception and performance, 19, 1238-1250, 1993.
Corbetta, M., Miezin, F.M., Dobmeyer, S., Shulman, G.L. and Peterson, S.E. 1991. Selective and divided attention during visual discriminations of shape, color and speed: functional anatomy by positron emission tomography. J. Neurosci. 11, 2383-2402,1991
Corbetta, M., Miezin, F.M., Shulman, G.L. and Peterson, S.E. 1993 A PET study of visuospatial attention. J. Neurosci. 13, 1202-26, 1993.
Corbetta, M., Shulman, G.L., Miezin, F.M. and Peterson, S.E. 1995 Superior parietal activity during a conjunction visual search task. Supplement 1, p192, Human Brain Mapping first international conference on functional mapping of the human brain, 1995.
Coren, S., Ward, L.M. and Enns, J.T. 1994 (Eds.) Sensation and Perception. 4th edition. Harcpurt Brace, 1994
Corletto, F., Gentilomo, A., Rosadini, G., Rossi, G.F., Zattoni, J. 1967 Visual evoked potentials as recorded from the scalp and from the visual cortex before and after surgical removal of the occipital pole in man. Electroencephalography and clinical Neurophysiology, 22, 378-380, 1967.
Costa, D.C., Ell, P.J., Burns, A., Philpot, M. and Levy, R. 1988 CBF tomograms with (Tc 99M-HM-PAO) in patients with dementia (Alzheimer type and HIV) and Parkinson's disease: Initial results. J. of cerebral blood flow and metabolism, 8, (6), 5109-5115, 1988.
Cowan,N., Winkler, I., Teder, W. and Näätänen, R. 1993 Memory prerequisites of the mismatch negativity in the auditory event-related potential (ERP). J. of Experimental Psychology: Learning, Memory and Cognition, 19, 909-921, 1993.
Cowell, P.E., Turetsky, B.I., Bruce, I., Gur, R.C., Grossman, R.I., et al., 1994 Sex differences in aging of the human frontal and temporal lobes. J. of Neuroscience, 14 (8), 4748-4755, 1994.
Cox, T.A. and Parson Drewes, C. 1984 Contraction anisocoria resulting from half-field illumination. American J. of Ophthalmology 97; 577-582, 1984.
Crick, F. 1984 The function of the thalamic reticular complex: the searchlight hypothesis. Proc. Natl. Acad. Sci. USA 81, 4586-4590.
Cronin-Golomb, A., Corkin, S., Rizzo, J.F., Cohen., Growdon, J.H. and Banks, K.S. 1991 Visual dysfunction in Alzheimer's disease: relation to normal aging. Ann Neurol 1991: 29; 41-52.
Cronin Golomb, A., Sugiura, R., Corkin, S. and Growdon, J.H. 1993 Incomplete achromatopsia in Alzheimer's disease. Neurobiology of aging, 14, 471-477, 1993.

Cronin-Golomb, A., Corkin, S. and Growdon, J.H. 1995 Visual dysfunction predicts cognitive deficits in Alzheimer's disease. Optometry and Vision Science, 7, 168-176, 1995.
Csépe, V., Karmos, G. and Molnar, M. 1989 Effect of changes in stimulus frequency on auditory evoked potentials in awake and anaesthetized cats. In J.Horn and P.Lavie,(Eds.), Sleep '88 (210-211). Stuttgart: Gustav Fischer Verlag, 1989.
Csépe, V., Pantev, C., Hoke, M., Hampson, S. and Ross, B. 1992 Evoked magnetic responses of the human auditory cortex to minor pitch changes: localization of the mismatch field. Electroencephalography and clinical Neurophysiology, 48, 538-548, 1992.
Csépe, V., Pantev, C., Hoke, M., Ross, B. and Hampson, S. 1997 Mismatch field to tone pairs: neuromagnetic evidence for temporal integration at the sensory level. Electroencephalography and Clinical Neurophysiology, 104, 1-9, 1997.
Cummings, B.J. and Cotman, C.W. 1995 Image analysis of beta-amyloid load in Alzheimer's disease in relation to dementia severity. Lancet, 346, 1524-1528, 1995.
Curcio,C.A. and Drucker, D.N. 1993 Retinal ganglion cells in Alzheimer's disease and aging. Annals of Neurology, 33, 248-257, 1993.
Czigler, I. and Csibra, G. 1990 Event-related potentials in a visual discrimination task: negative waves related to detection and attention. Psychophysiology, Vol. 27, No. 6, 669-676, 1990.
Czigler, I. and Csibra, G. 1992 Event-related potentials and the identification of deviant visual stimuli. Psychophysiology, Vol.29, No.4, 471-485 1992.
Czigler, I. and Winkler 1996, cited in Schroger, 1997.

Damasio, A.R. 1985 disorders of complex visual processing: agnosias, achromatopsia, Balint's syndrome and related difficulties of orientation and construction. In: Mesulam, M.M. (Ed.) Principles of behavioral neurology. Contemporary neurology series. Philadelphia: F.A. Davis, 26, 259-2888, 1985.
Daniels, R., Harding, G.F.A., and Anderson, S.J. 1994 Effect of dopamine and acetylcholine on the visual evoked potential. International J. of Psychophysiology 16, 251-161, 1994.
Davies, C.A., Mann, D.M.A., Sumpter, P.Q. 1987 A quantitative morphometric analysis of the neuronal and synaptic content of the frontal and temporal cortex in patients with Alzheimer's disease. J. of Neurological Science, 78, 151-164, 1987.
DeCarli, C., Murphy, D.G.M., Gillette, J.A., Haxby, J.V., Teichberg, D., Schapiro, M.B., Horwitz, B. 1994 Lack of age-related differences in temporal lobe volume of very healthy adults. American J. of Neuroradiology, 15, 689-696, 1994.
Della Sala, S., Muggia, S., Spinnler, H and Zuffi, M. 1995 Cognitive modelling of face processing: evidence for Alzheimer patients. Neuropsychologia, 33 (6), 675-687, 1995.
Della Sala, S., Laicona, M., Spinnler, H., and Ubezio, C. 1992 A cancellation test: its reliability in assessing attentional deficits in Alzheimer's disease. Psychology and Medicine, 22, 885-901, 1992.
de Monasterio and Gouras 1975 cited in Schiller and Logothetis, 1990..
de Montasterio 1978 cited in Bruce et al 1997.
Derrington, A.M. and Lennie, P. 1984 Spatial and temporal contrast sensitivities of neurons in lateral geniculate nucleus of macaque. J. of Physiology, 357, 219-240, 1984.
Desimone, R. and Ungerleider, L.G. 1989 Neural mechanisms of visual processing in monkeys. In Handbook of Neurophsychology, Vol.2, ed. F Boller, J. Grafman, pp. 267-299. New York: Elsevier, 1989.
Desimone, R., Schein, S.J., Moran, J. and Ungerleider, L.H. 1985 Contour, color and shape analysis beyond the striate cortex. Vis. Res.25, 441-452, 1985.
Desimone, R. and Duncan, J. 1995 Neural mechanisms of selective visual attention. Annu. Rev. Neurosci. 18, 193-222, 1995.
Desimone, R. Albright, T.D., Gross, C.G. and Bruce, C. 1984 Stimulus-selective properties of inferior temporal neurons in the macaque. J. Neurosci. 4, 2051-2062, 1984.
Deutsch, J.A. and Deutsch, D. 1963 Attention: some theoretical considerations. Psychol. Rev. 70, 80-90, 1963.
DeValois, R.L., Albrecht, D.G. and Thorell, L.G. 1982 Spatial frequency selectivity of cells in macaque visua; cortex. Vision Research, 22, 545-559, 1982.
De Valois, R.L. and DeValois, K.K. 1990 Spatial Vision, oxford University Press, 1990, chp.1.
Dewer, D. and McCulloch, J. 1994 Abnormalities in non-cholinergic neurotransmitter systems in Alzheimer's disease. In 'Dementia.' Edited by A. Burns and R. Levy, 1994, Chapman and Hall, London.

De Yoe, E.O. and Van Essen, D.C. 1985 Segregation of efferent connections and receptive field properties in visual area V2 of the macaque. Nature, 317, 58-61, 1985.
DeYoe, E.A. and Van Essen, D.C. 1988 Concurrent processing streams in monkey visual cortex. TINS, 11, 219-226, 1988.
Distler, C., Weigel, H., Hoffman, K.P. 1993 Glial cells of the monkey retina. I. Astrocytes. J. of Comparative Neurology, 333, 134-147, 1993.
Donchin, E., Ritter, W. and McCallum, W.C. 1978 Cognitive psychophysiology: the endogenous components of ERP. In E. Calloway, P.Tueting and S.H. Koslow (Eds.), Event related brain potentials in man (pp349-411). New York: Academic Press, 1978.
Drachman, D.A. and Levitt, J. 1974 Human memory and the cholinergic system: a relationship to ageing. Archives of Neurology, 30, 113-121, 1974.
Dreher et al 1976 cited in Bruce et al 1997.
Drischel 1957 cited in Barbur and Forsyth, 1986.
Drucker, D.N. and Curcio, C.A. 1993 Retinal ganglion cells in Alzheimer's disease and aging. Annals of Neurology, 33, 248, 1993.
Drysdale, K.A., Finlay, D.C. and Fulham, W.R. 1995 An event-related potential examination of attended and unattended stimuli in visual selection using bilateral stimulus presentation. Biological Psychology 39, 1995, 115-129.
DSM-IV 1994 cited in Lezak 1995.
Duara, R., Barber, W., Loewenstein, D., Pascal., S. and Bowen, B. 1990 sensitivity and specificity of PET and MRI studies in AD and MID. European Neurology, 29 (53), 9-15, 1990.
Ducati, A., Fava, E. and Motti, E.D.F. 1988 Neuronal generators of the visual evoked potentials: intracerebral recordings in awake humans. Electroencephalogra[hy and Clinical Neurophysiology, 71, 89-99, 1988.
Duffy, C.J. and Wurtz, R.H. 1991 Sensitivity of MST neurons to optic flow stimuli. J. of Neurophysiology, 65 (6), 1346-1359, 1991.
Duncan, J. 1980 The locus of interference in the perception of simultaneous stimuli. Psychol. Rev. 87, 272-300, 1980.
Duncan, J. and Humphreys, G.W. 1989 Visual search and stimulus similarity. Psychol. Rev. 96:433-458, 1989.

Eberling, J.L., Jagust, W.J., Reed, B.R., Kwo-on-Yuen, P.F. and Martin, E.M. 1992 Single-photon emission computed tomography studies of regional cerebral blood flow in multiple infarct dementia. J. Neuroimaging, 2, 79-85, 1992.
Eberling, J.E., Richardson, B.C., Reed, B.R., Wolfe, N. and Jagust, W.J. 1994 Cortical glucose metabolism in Parkinson's disease without dementia. Neurobiology of aging, 15, 3, 329-335, 1994.
Elston, G.N. and Rosa, M.G.P. 1997 The occipito-parietal pathwauy of the macaque monkey: comparison of pyramidal cell morphology in layer III of functionally related cortical visual areas. Cerebral cortex, 7, 432-452, 1997.
Emmerson-Hanover, R., Shearer, D.E., Creel, D.J. and Dustman, R.E. 1994 Pattern reversal evoked potentials: gender differences and age-related changes in amplitude and latency. Electroencephalography and clinical Neurophysiology, 92, 93-101, 1994.
Engel, A.K., Kreiter, A.K. and Singer, W. 1992 Oscillatory responses in the superior temporal sulcus of anaesthetized macaque monkeys. Society. Neuroscience Abstracts, 18 (11), p.10, 1992.
Engel, S.A., Glovel, G.H. and Wandell, B.A. 1997 Retinotopic organization in human visual cortex and the spatial precision of functional MRI. Cerebral Cortex, 7, 181-192, March, 1997.
Enns, J.T. and Rensink, R.A. 1991 Preattentive recovery of three dimensional orientation from line drawings. Psychological Review, 98, 335-351, 1991.
Erikson, C.W. and St. James, J.D. 1986 Visual attention within and around the field of focal attention:a zoom lens model.Perception and Psychophysics, 45, 175-183, 1986.

Faust, M.E. and Balota, D.A. 1997 Inhibition of return and visuospatial attention in healthy older adults and individuals with dementia of the Alzheimer type. Neuropsychology, 11, 1, 13-29, 1997.
Felleman, D.J. and Van Essen, D.C. 1991 Distributed hierarchical processing in the primate cortex. Cerebral Cortex, 1, 1-47, 1991.

Ferrera, V.P., Nealy, T.A. and Maunsell, J.H.R. 1994 Responses in macaque visual area V4 following inactivation of the parvocellular and magnocellular LGN pathways. J. of Neuroscience, 14, 2080-2088, 1994.
ffytche, D.H., Guy, C.N. and Zeki, S. 1995 Motion specific responses from a blind hemifield. Brain, 119, 1971-1982, 1996.
Fibiger, H. C. 1991 Cholinergic mechanisms in learning, memory and dementia: a review of recent evidence. TINS, Vol.14, N0.6, 220-223, 1991.
Filooteo, J.V., Delis, D.C., Massman, P.J., Demadura, T., Butters, N. and Salmon, D.P. 1992 Directed and divided attention in Alzheimer's disease: impairment in shifting of attention to global and local stimuli. J. of Clinical and Experimental neuropsychology, 14, 871-883, 1992.
Finch 1994 In Raz et al., 1997.
Fisher, L.M., Freed, D.M. and Corkin, S. 1990 Stroop colo-word test performance in patients with Alzheimer's disease. J. of Clinical and Eperimental Neuropsychology, 12, 5, 745-758, 1990.
Fitzpatrick and Raczzkowski, 1991. Cited in Hasselmo and Bower, 1993.
FitzSimon, J.S., Waring, S.C., Kokmen, E., McLaren, J.W. and Brubaker, R.F. 1997 response of the pupil to Tropicamide iv not a reliable test for Alzheimer's disease. Archives of Neurology, 54, 155-159, Feb., 1997.
Fletcher, W.A. and Sharpe, J.A. 1986 Saccadic eye movement dysfunction in Alzheimer's disease. Annals of Neurology, 20, 464-471, 1986.
Fletcher, W.A. and Sharpe, J.A. 1988 Smooth pursuit dysfunction in Alzheimer's disease. Neurology, 38, 272-277, 1988.
Folk, C.L. and Lincourt, A.E. 1996 The effects of age on guided conjunction search. Experimental aging research, 22, 99-118, 1996.
Forrester, J., Dick, A., McMenamin, P. and Lee, W. 1996 The Eye, pp.207-209. WB Saunders Company Ltd, 1996,
Förstl, H., Hentschel, F., Sattel, H., Geuigerkabisch, C., Besthorn, C., Czech, C., Monning, J.J and Beyreuther, K. 1995 Age associated memory impairment and early Alzheimer's disease- only time will tell the difference. Drug Research, 45 (1), 394-397, 1995.
Fratiglioni, L., Viitanen, M., von Strauss, E., Tontodonati, V., Herlitz, A. and Winblad, B. 1997 Very old women at highest risk of dementia and Alzheimer's disease: incidence data from the Kungsholmen project, Stockholm. Neurology, 48, 132-138, 1997.
Friston, K.J., Ungerleider, L.G., Jezzard, P. and Turner, R. 1995 characterizing modulatory interactions between areas v1 and V2 in human cortex: A new treatment of functional MRI data. Human Brain Mapping 2: 211-224, 1995.

Gabella, G. 1991 The sphincter pupillae. In T. Tomita and E. Daniel (Eds.) Sphincters: Normal Function - Changes in diseases, CRC Press, Boca Raton, FL, 1991.
Gaillard, A.W.K. 1988 Problems and paradigms in ERP research. Biological Psychology, 26, 91-109, 1988.
Gaillard and Ritter 1983 (Eds.) Tutorials in ERP research: endogenous components. Amsterdam: North-Holland Publishing Company, 1983.
Galasko, D., Hansen, L.A., Katzman, R., Wiederholt, W., Masliah,E., Terry, R., Hill, L.R. Lessin, P. and Thal, L.J. 1994 Clinical-neuropathological correlations in alzheimer's disease and related dementias. Arch. Neurol., Vol. 51, Sep. 1994
Geaney, D.P. and Abou-Saleh, M.T. 1990 The use and application of SPECT in dementia. British J. of Psychiatry, 157, (59), 66-75, 1990.
Geesaman, B.J. and Anderson, R.A. 1996 The analysis of complex motion patterns by form/cue invariant MSTd neurons. J. Neuroscience, 16, 4716-4732, 1996.
Geula, C. and Mesulam, M. 1996 Systematic regional variations in the loss of cortical cholinergic fibers in Alzheimer's disease. Cerebral Cortex, 6, 165-177; 1047-3211, 1996.
Giard, M.H., Perrin, F. and Pernier, J. 1990 Brain generators implicated in processing of auditory stimulus deviance: a topographical ERP study. Psychophysiology, 1990, 27, 627-640, 1990.
Giard, M.H., Collet, L., Bouchet, P. and Pernier, J. 1994 auditory selective attention in the human cochlea. Brain Research, 633, 353-356, 1994.
Giard, M.H., Lavikainen, J., Reinnikainen, K., Perrin, F., Bertrand, O., Pernier, J. and Naatanen, R. 1995 Separate representation of stimulus frequency, intensity and duration in auditory

sensory memory: an event-related potential and dipole-model analysis. J. of Cognitive Neuroscience, &, 133-143, 1995.

Gilchrist, I.D., Humphreys, G.W., Neumann, H. and Riddoch, M.J. 1997 Luminance and Edge information in Grouping: a study using visual search. J. of Exoperimental Psychology: Human Perception and Performance, 23, 2, 464-480, 1997.

Gilmore, R. 1995 Evoked potentials in the elderly. J. of Clinical Neurophysiology, 12 (2):132-138, 1995.

Golan, H., Kremer, J., Freedman, M. and Ichise, M. 1996 Usefulness of follow-up regional cerebral blood flow measurements by single-photon emission computed tomography in the differential diagnosis of dementia. J. Neuroimaging, 6, 23-28, 1996.

Goldsmith, S.K. and Joyce, J.N. 1995 Alterations in hippocampal mossy fibre pathway in schizophrenia and Alzheimer's disease. Biological Psychiatry, 37 (2), 122-126, 1995.

Gómez-Isla, T., Hollister, R., West, H., Mui, S., Growdon, J.H., Peterson, R.C., Parisi, J.E., and Hyman, B.T. 1997 Neuronal loss correlates with but exceeds neurofibrillary tangles in Alzheimer's disease. Ann. Neurology, 41; 17-24, 1997.

Goodale, M.A. and Milner, A.D. 1991 A neurological dissociation between perceiving objects and grasping them. Nature, 349, 154-156, 1991.

Goodin, G.S. and Aminoff, M.J. 1992 Evaluation of dementia by event-related potentials. J. of Clinical Neurophysiology, 9 (4); 521-525, 1992.

Goto, I., Taniwaki, T., Hosokawa, S., Otsuka, M., Ichiya, Y. and Ichimiya, A. 1993 Positron emission tomographic (PET) studies in dementia. J. of the Neurological Sciences, 114 (1993) 1-6.

Grady, G.L., Haxby, J.V., Horwitz, B., Sundaram, M., Berg, E., Schapiro, M., Friedland, R.P. and Rapoport, S.I. 1988. Longitudinal study of the early neuropsychological and cerebral metabolic changes in dementia of the Alzheimer's type. J. of Clinical and Experimental Neuropsychology, 10, 576-596, 1988.

Grande, L., McGlinchey-Berroth, R., Milberg, W.P. and D'Esposito, M. 1996 Facilitation of unattended semantic information in Alzheimer's disaese: evidence from a selective attention task. Neuropsychology, 10, 4, 475-848, 1996.

Gray, C.M., König, P., Engel, A.K. and Singer, W. 1989 Oscillatory responses in cat visual cortex exhibit inter-columnar synchronization which reflects global stimulus properties. Nature, 338, 334-337, 1989.

Greenlee, M.W., Koessler, M., Cornelissen, F.W. and Mergner, T. 1997 visual discrimination and short term memory for random patterns in patients with a focal cortical lesion. Cerebral Cortex, 253-267, Apr/May, 1997.

Greenwood, P.M. and Parasuraman, R. 1994 Attentional disengagement deficit in nondemented elderly over 75 years of age. Aging and Cognition, 1 (3), 188-202, 1994.

Greenwood, P.M., Parasuraman, R. and Alexander, G.E. 1997 controlling the focus of spatial attention during visual search: effects of advanced aging and Alzheimer's disease. Neuropsychology, 11, 1, 3-12, 1997.

Grewal, B.S. 1989 Perceptual deficits in Alzheimer's disease. Medical Scientific research, 17, 51-52, 1989.

Gross, M.M., Begleiter, H., Tobin, M. and Kissin, B. 1966 Changes in auditory evoked responses induced by alcohol. J. of Nervous and Mental Disease, 143, 152—156, 1966.

Grossberg, S., Mingolla, E, and Ross, W.D. 1994 A neural theory of attentive visual search: interactions of boundary, surface, spatial and object representations. Psychol. Rev. 101, ?-? ****

Growdon, J.H, Graefe, K., Tennis, M., Hayden, D., Schoenfeld, D. and Wray, S.H. 1997 Pupil dilation to Tropicamide is not specific for Alzheimer's disease. Archives of Neurology, 54, 841-844, 1997.

Guido and Lu 1995. Cited in Nobilinand Sannita, 1997.

Gunter, T.C., Wijers, A. A., Jackson, J.L.J. and Mulder, G. 1994 visual spatial attention to stimuli presented on the vertical and horizontal meridian: an ERP study. Psychophysiology, 31 (1994), 140-153.

Hackley, S.A. 1993 An evaluation of the automaticity of sensory processing using event-related potentials and brain-stem reflexes. Psychiphysiology, 5, 415-428, 1993.

Hackley, S.A., Woldorff, M. and Hillyard, S.A. 1990 Cross-modal selective attention effects on retinal, myogenic, brainstem and cerebral evoked potentials. Psychophysiology, 27, 2, 195-208, 1990.

Haenny, P.E. and Schiller, P.H. 1988 State dependent activity in visual cortex I; single cell activity in V1 and V4 on visual tasks. Experimental Brain Research, 69, 225-244, 1988.
Hagan, J.J. and Morris, R.G.M. 1988 In Handbook of Psychopharmacology, 20, (Eds. Iverson, L.L., Iverson, S.D. and Snyder, S.H.), pp. 237-324. Plenum Press New York, 1988.
Halliday, A.M. 1982 Evoked potentials in clinical testing,. London: Churchill Livingstone, 1982.
Hardy, J. 1997 Amyloid, the presenilins and Alzheimer's disease. TINS, vol, 20, No.4, 154-159, 1997.
Hari, R., Hämäläinen, Ilmoniemi, R., Kaukoranta, E., Reinikainen, K., Salminen, J., Alho, K., Näätänen. R. and Sams, M. 1984 Responses of the primary auditory cortex to pitch changes in a sequence of tone pips: Neuromagnetic recording in man. Neuroscience letters, 50, 127-132.
Hari, R., Sams, M. and Jarviilehto, T. 1979 Auditory evoked transient and sustained potentials in the human EEG: II: effects of small doses of ethanol. Psychiatry research, 1, 307-312, 1979.
Harpur, L.L., Scialfa, C.T. and Thomas, D.M. 1995 Age differences in feature search as a function of exposure duration. Experimental Aging Research, 21, 1-15, 1995.
Harrington, C.R. and Wischik, C.M. 1994 The impact of genetic and envirobmental factors on the pathology of Alzheimer's disease: a multifactorial disorder ? International review of Psychiatry, 7 (3), 361-384, 1995.
Harris, W.S. and Goodman, R.M. 1968 Hyper-reactivity to atropine in Down's syndrome. New England J. of Medicine, 279, 407-410, 1968.
Harris, J.P., Calvert, J.E. and Phillipson, O.T. 1993 Processing of spatial contrast in peripheral vision in Parkinson's disease.
Hart, S. and Semple, J.M. 1990 Neuropsychology and the Dementias, Chapter 10; Attention. Edited by S. Hart and J.M. Semple; Taylor and Francis, 1990.
Harter, M.R. and Anllo-Vento, L. 1990 Modality differences: memory trace development or efferent cortical priming ? Behavioral and Brain Sciences, 13, 243-244, 1990.
Harter, M.R. and Anllo-Vento, L. 1991 Visual-spatial attention: preparation and selection in children and adults. In C.H.M. Brunia, G. Mulder and M.N. Verbaten (Eds), Event-related potentials of the brain, pp. 183-194. Supplement 42 to Electroencephalography and Clinical Neurophysiology, Amsterdam: Elsevier, 1991.
Harter, M.R. and Guido, W. 1980 Attention to pattern orientation: negative cortical potentials, rection time and the selection process. Electroencephalography and Clinical Neurophysiology, 49, 461-475, 1980.
Harter, M.R. and Previc, F.H. 1978 Size-specific information channels and selective attention: visual evoked potential and behavioral measures. Electroencephalography and Clinical Neurophysiology, 45, 628-640, 1978.
Harter, M.R. and Salmon, L.E. 1972 Intra-modality selective attention and evoked cortical potentials to randomly presented patterns. Electroencephalography and Clinical Neurophysiology, 32, 605-613, 1972.
Hashikawa, K., Matsumoto, M., Moriwaki, H., oku, N., Okazaki, Y., Seike, Y., Uehara, Y., Tanabe, H., Ohie, Y., Kamada, T. and Nishimura, T. 1995 3-dimensional dispaly of surface cortical perfusion by SPECT-application in assessing Alzheimer's disease. J. of Nuclear medicine, 36 (4), 690-696, 1995.
Hasselmo, M.E. and Bower, J.M. 1993 Acetylcholine and memory. TINS, 16 (6), 218-222, 1993.
Haxby, J.V., Grady, C.L., Duara, R., Schlageter, N., Berg, G. and Rapoport, S.I. 1986 Neocortical metabolic abnormalities precede non-memory cognitive defects in early Alzheimer's-type dementia. Arch. Neurol, 43, 882-885, 1986.
Haxby, J.V., Parasuraman, R., Gillette, J. and Raffaele, K. 1991 Selective and divided attention to visual features are impaired in patients with early dementia of the Alzheimer's type. Society for Neuroscience Abstracts, 17, 696, 1991.
Heathcote, A. and Mewhort, D.J.K. 1993 Representation and selection of relative position. J. of Experimental psychology: Human Perception and Performance, 1993, Vol. 19, No.3, 488-516.
Heinze, H.J., Mangun, G.R., Burchert, W., Hinrichs, H., Scholz, M., Münte, T.F., Gös, A., Scherg, M., Johannes, S., Hundeshagen, H., Gazzaniga, M.S. and Hillyard, S.A. 1994 Combined spatial and temporal imaging of brain activity during visual selective attention in humans. Nature, Vol. 372, 543-546, 8 December 1994.
Heinze, H.J., Luck, S.J., Mangun, G.R. and Hillyard, S.A. 1990 Visual event-related potentials index focused attention within bilateral stimulus arrays. I. evidence for early selection. Electroencephalography and Clinical Neurophysiology, 1990, 75: 511-527.

Heinze, H., Munte, T.F., Gobiet, W., Niemann, H. and Ruff, R.M. 1992 parallel and serial visual search after closed head injury: electrophysiological evidence for perceptual dysfunctions. Neuropsychologia, Vol. 30, No.6, 495-514, 1992.
Helson, G. 1964 Adaptation-level theory: an experimental and systematic approach to behaviour, Harper and Row, 1964.
Herholz, K. 1995 Report on the meeting on the multicentre study on accuaracy of PET in Alzheimer's disease. European J. of Nuclear medicine, 22 (9), p. 25, 1995.
Hillyard, S.A. 1981 Selective auditory attention and early event-related potentials: A rejoinder. Canadian J. of Psychology, 35, 85-100, 1981.
Hillyard, S.A. 1993 Electric and magnetic brain recordings: contributions to cognitive neuroscience. Current opinion in neurobiology, 3, 217-224, 1993.
Hillyard, S.A. and Münte, T.F. 1984 Selective attention to color and location: an analysis with event-related brain potentials. Perception and Psychophysics, 36, 185-198, 1984.
Hillyard, S.A., Münte, T.F. and Neville, H.J. 1985 Visual-spatial attention, orienting and brain physiology. In M.I. Posner and O.S. Marin (Eds.), Attention and Performance XI, Mechanisms of attention, pp.63-84. Hillsdale, NJ, Erlbaum, 1985.
Hillyard, S.A., Hink, R.F., Schwent, V.L. and Picton, T.W. 1973 Electrical signs of selective attention in the brain. Science, 182, 177-182, 1973.
Hillyard, S.A., Mangun, G.R., Woldorff, M.G. and Luck, S.J. 1995 Neural systems mediating selective attention. In M.S. Gazzaniga (Ed.) The cognitive neurosciences, pp. 665-681. Cambridge MA: The MIT press.
Hillyard, S.A., Hinrichs, H., Tempelmann, C., Morgan, S.t., Hansen, J.C., Scheich, H., Heinze, H.J. 1997 Combining steady state VEPs and fMRI to localize brain activity during selective attention. Human brain mapping, 5, 287-292, 1997.
Hinton, D.R., Sadun, A.A., Blanks, J.C., and Miller, C.A. 1986 Optic nerve degeneration in Alzheimer's disease. New England J. of Medicine, 315, 485-487, 1986.
Hof , P.R., Bierer, L.M., Perl, D.P., Delacourte, A., Buee, L., Bouras, C. and Morrison, J.H. 1992 Evidence for early vulnerability of the medial and inferior aspects of the temporal lobe in an 82 year old patient with preclinical signs of dementia. Arch. Neurol. 49, 946-953, 1992
Hof, P.R. and Bouras, C. 1991 Object recognition in Alzheimer's disease: possible disconnection of the occipito-temporal component of the visual system. Neuroscience Letters, 122, 53-56, 1991.
Hof, P.R. and Morrison, J.H. 1990 Quantitative analysis of a vulnerable subset of pyramidal neurons in Alzheimer's disease: I. Superior frontal and inferior temporal cortex. J. of Comparative Neurology, 301, 44-54, 1990.
Hof, P.R., Vogt, B.A., Bouras, C. and Morrison, J.H. 1997 A typical form of Alzheimer's disease with prominent posterior cortical atrophy: a review of lesion distribution and circuit disconnection in cortical visual pathways. Vision Research, 37 (24), 3609-3625, 1997.
Hoffman, J.E., Nelson, B. and Houck, M.R. 1983 The role of attentional resources in automatic detection. Cognitive Psychology, 15, 379-410, 1983.
Hosegowa and Aoba 1994
Hubbard, B.M. and Squier, M. 1989 The physical ageing of the neuromuscular system; chapter one in The Clinical Neurology of Old Age, edited by R. Tallis, 1989. John Wiley and Sons Ltd.
Hubel, D.H. and Livingstone, M.S. 1987 Segregation of form, color and stereopsis in primate area 18. J. of Neuroscience, 7, 3378-3415, 1987.
Hubel, D.H. and Wiesel, T.N. 1959 Receptive fields of single neurons in the cat's striate cortex. J. of Physiology, 148, 574-591, 1959.
Hubel, D.H. and Wiesel, T.N. 1962 Receptive fields, binocular interaction and functional architecture in the cats visual cortex. J. of Physiology, 160, 106-154, 1962.
Hubel, D.H. and Wiesel, T.N. 1968 Receptive fields and functional architecture of monkey striate cortex. J. of Physiology, 193, 215-243, 1968.
Hubel, D.H. and Wiesel, T.N. 1970 Cells sensitive to binocular depth in area 18 of the macaque monkey cortex. Nature, 225, 41-42, 1970.
Hunter, S. 1985 The rostral mesencephalon in Parkinson's disease and Alzheimer's disease. Acta Neuropathologica, 68, (1), 53-58, 1985.
Hutton, J.T., Morris, J.L., Elias, J.W. and Poston, J.N. 1993 Contrast sensitivity dysfunction in Alzheimer's disease. Neurology, 43, 2328-2330, 1993.

Hutton, J.T., Nagel, J.A. and Loewenson, R.B. 1984 Eye tracking dysfunction in Alzheimer-type dementia. Neurology, 34, 99-102, 1984.
Hyman, B.T., Arriagada, P.V., Van-Hoesen, G.W. and Damasio, A.R. 1993 Memory impairment in alzheimer's disease: an anatomical perspective in R.W. Park and F. Ronald, (eds.) Neuropsychology of Alzheimer's disease and other dementias, pp. 138-150****need publisher
Hyönä, J., Tommola, J. and Alaja, A. 1995 Pupil dilation as a measure of processing load in simultaneous interpretation and other language tasks. The Quarterly J. of Experimental Psychology, 48 (A) (3), 598-612, 1995.

Idiaquez, J., Alvarez, G., Villagra, R. and San Martin, R.A. 1994 Cholinergic supersensitivity of the iris in Alzheimer's disease [letter]. J. Neurology, Neurosurgery and Psychiatry, 57, 1544-1545, 1994.
Ichikawa, T. and Shimizu, T. 1998 Organization of choline acetyltransferase-containing structures in the cranial nerve motor nuclei and spinal cord of the monkey. Brain research, 779 (1-2), 96-103, Jan. 1., 1998.
Iyo, M., Namba, H., Fukushi, K., Shinotoh, H., Nagatsuka, S., Suhara, T., Sudo, Y., Suzuki, K. and Irie, T. 1997 Measurement of acetylcholinesterase by positron emission tomography in the brains of healthy controls and patienst with Alzheimer's disease. The Lancet, vol 349, 1805-1809, 1997.

Jääskeläinen, I.P., Pekkonen, E., Hirvonen, J., Sillanaukee, P. and Näätänen, R. 1996 Mismatch negativity subcomponents and ethyl alcohol. Biological Psychology, 43, 13-25, 1996.
Jääskeläinen, Lehtokoski, Alho, Kujalla, Pekkonen, Sinclair, Naatanen and Sillanaukee (in press) cited in Jaaskelainen et al 1996.
Jack, C.R., Peterson, R.C., O'Brien, P.C. and Tangalos, E.G. 1992 MR-based hippocampal volumetry in the diagnosis of Alzheimer's disaese. Neurology 42, (1), 183-188, 1992.
Jagust, W.J., Reed, B.R., Seab, J.P. and Budinger, T.F. 1990 Alzheimer's disease - age at onset and SPECT patterns of regional cerebral blood flow. Archives of Neurology, 47 (6), 628-633, 1990.
Javitt, D.C., Doneshka, P., Zylberman, I., Ritter, W., et al., 1993 Impairment of early cortical processing in schizophrenia: an ERP confirmation study. Biological Psychiatry, 33 (7), 513-519, 1993.
Javitt, D.C., Doneshka, P., Grochowski, S. and Ritter, W. 1995 Impaired mismatch negativity generation reflects widespread dysfunction of working memory in schizophrenia. Archives of General Psychiatry, 52 (7), 550-558, 1995.
Jeffries, D.A. 1996 Visual evoked potential evidence for parallel processing of depth and form-related information in human visual cortex. Experimental Brain Research, 111, 79-99, 1996.
Jernigan, T.L., Archibald, S.L., Berhow, M.T., Sowell, E.R., Foster, D.S. and Hesselink, J.R. 1991 Cerebral structure on MRI, part I: localization of age-related changes. Biological Psychiatry, 29, 55-67, 1991.
Jessel 1991
Joachim, C.L., Mori, H. and Selkoe, D.J. 1989 duffuse senile plaques occur commonly in the cerebellum in Alzheiemr's disease. American J. of Pathology, 135 (2), 309-319, 1989.
Jobst, K.A., Smith, A.D., Szatmari, M., Molyncux, A., Esiri, M.E. and King, E. 1992 Detection in life of confirmed Alzheimer's disease using a simple measurement of medial temporal lobe atrophy by computed tomography. The Lancet, 340, 1179-1183, 1992.
Johnston, W.A., and Dark, V.J. 1986 Selective attention. Annual Review of Psychology, 37, 43-75, 1986.
Johnston, W.A., Hawley, K.J. and Farnham, J.M. 1993 Novel Popout: empirical boundaries and tentative theory. J. of Experimental Psychology: Human Perception and Performance, 19, 140-153.
Jonides, J., Smith, E.E., Koeppe, R.A. Awh, E., Minoshima, S. and Mintun, M.A. 1993 Spatial working memory in humans as revealed by PET. Nature, 363, 623-625, 1993.
Jonides, J. and Yantis, S. 1988 Uniqueness of abrupt visual onset in capturing attention. Perception and Psychophysics, 43, 346-354, 1988.
Julesz, B. 1975 Experiments in the visual perception of texture. Scientific American, 232, 34-43, 1975.
Juncos, J.L., Hirsch, E.C., Malessa, S., Duyckaerts, C., Hersh, L.B. and Agid, Y. 1991 Mesencephalic cholinergic nuclei in progressive supranucleaar palsy. Neurology, 41 (1), 25-30, Jan., 1991.
Just, M.A. and Carpenter, P.A. 1993 The intensity dimension of thought: pupillometric indices of sentence processing. Canadian J. of Experimental Psychology, 47:2, 310-339, 1993.

Kahneman, D. 1973 Attention and Effort. Engelwood Cliffs, NJ:Prentice Hall, 1973.
Kahneman, D. and Treisman, A. 1984 Changing views of attention and automaticity. In Parasuraman, R., Davies, R. and Beatty, (Eds.) Varieties of attention, pp.29-61. New York: Academic Press.
Kalman, J., Kanka, A., Maglóczky, E., Szóke, A., Jardanhazy, T. and Janka, Z. 1997 Increased mydriatic response to Tropicamide is a sign of cholinergic hypersensitivity but not specific to late-onset sporadic type of Alzheimer's deficit. Biol. Psychiatry, 41, 909-911, 1997.
Kane, N.M., Curry, S.H., Butler, S.R. and Cummins, B.H. 1993 Electrophysiological indicator of awakening from coma. The Lancet, 341, p688, March 13, 1993.
Kaplan, E., Lee, B.B and Shapley, R.M. 1990 New views of primate retinal function. Progr. Retinal Res., 9, 273-336, 1990.
Karayanidis, F. and Michie, P.T. 1996 Frontal processing negativity in a visual selective attention task, Electroencephalography and Clinical Neurophysiology, 99, 38-56, 1996.
Kardon, R.H., Kirkall, P.A. and Thompson, H.S. 1991 Automated pupil perimetry. Pupil field mapping in patients and normal subjects. Ophthalmology, 98, 485-496, 1991.
Kastner, S., Nothdurft, H-C., and Pigarev, I.N. 1997 Neuronal correlates of pop-out in cat striate cortex. Vision Research, 37, 371-376, 1997.
Katz, B. 1995 Detecting Alzheimer's disease [letter]. Science, 267, (5204), 1578-1581, 1995.
Katz, B., Rimmer, S., Iragui, V. and Katzman, R. 1989 Abnormal pattern electroretinogram in Alzheimer's disease: evidence for retinal ganglion cell degeneration ? Annals of Neurology, 26, 221-225, 1989.
Katzman, R. 1986 Alzheimer's disease. New England J. of Medicine, 314, 964-973, 1986.
Kawashima, S., Tabuchi, A. and Matsuda, K. 1992 Analysis of the generators of the flash and pattern reversal middle latency visual evoked potentials by composite image diagnosis. Japanese J. of Electroencephalography and Electromyography, 20, 53-62, 1992.
Keilp, G.K. and Prohovnik, I. 1995 Intellectual decline predicts the parietal perfusion deficit in Alzheimer's disease. J. Nucl. Med. 36; 1347-1354, 1995.
Kemper, T.L. 1994 Neuroanatomical and neuropathological changes during aging and dementia. In A. Martin and J.E. Knoefel (Eds) Clinical Neurology of aging (2 nd ed.), New York, Oxford University Press, pp. 3-67, 1994.
Kertesz, A. 1994 (Ed.) Localization and Neuroimaging in neuropsychology. Academic Press, San Diego, 1994.
Kiyosawa, M., Baron, J.C., Hamel, E., Pappata, S., Duverger, D, Riche, D., Mazoyer, B., Naquet, R. and MacKenzie, E.T. 1989 Time course of effects of unilateral lesions of the nucleus basalis of Meynert on glucose utilization by the cerebral cortex: positron tomography in baboons. Brain, 112, 435-455, 1989.
Kleffner, D. and Ramachandran, V. 1992 On the perception of shape from shading. Perception and Psychophysics, 52, 18-36, 1992.
Klekkoy 1976
Knierim, J.J, and Van Essen, D.C. 1992 Neuronal responses to static texture patterns in area V1 of the alert macaque monkey. J. Neurophysiology, 67, 961-980.
Kohn, M. and Clynes, M. 1969 Colour dynamics of the pupil. Annals of the New York Acadamy of Science, 156, 931-950, 1969.
Kraus, N., McGee. T., Micco, A., Carrell, T., Sharman, A. and Nicol, T. 1993 Mismatch negativity in school-age children to speech stimuli that are just perceptibly different. Electroencephalography and Clinical Neurophysiology, 88, 123-130, 1993.
Kraus, N., McGee, T., Littman, T., Nicol, T. and King, C. 1994 (a) Encoding of acoustic change involves non-primary auditory thalamus. J. of Neurophysiology, 72, 1270-1277, 1994.
Kraus, N., McGee, T., Carrell, T., Littman, T. and Nicol, T. 1994 (b) Discrimination of speech-like signals in auditory thalamus and cortex. J. of Acoustical Society of America, 96, 2758-2768, 1994.
Kuffler, S.W. 1953 Discharge patterns and functional organization of mammalian retina. J. Neurophysiology, 16, 37-68, 1953.
Kumar, A., Schapiro, M.B., Grady, C., Haxby, J.V., Wagner, E., Salerno, J.A., Friedland, R.P. and Rapoport, S.I. 1991 High resolution PET studies in Alzheimer's disease. Neuropsychopharmacology, 4, 35-46, 1991.
Kurtzberg, D., Vaughan, H.G., Kreuzer, J.A. and Fliegler, K.Z. 1995 Developmental studies and clinical applications of mismatch negativity: problems and prospects. Ear and Hearing, 16, 105-117, 1995.

Kurtzberg, Kreuzer, Fleigletr, Ritter and Vaughan 1996, cited in Schröger, 1997.
Kurylo, D.D,. Corkin, S., Dolan, R.P., Rizzo, J.F., Parker, S.W. and Growdon, J.H. 1994 broad-band visual capacities are not selectively impaired in Alzheimer's disease. Neurobiology of aging, Vol. 15, No.3, 305-311, 1994.
Kurylo, D.D., Corkin, S., Rizzo, J.F. and Growdon 1996 Greater relative impairment of object recognition. Neuropsychology, Vol. 10, No. 1, 74-81, 1996.
Kushner, M.J., Rosenquist, A., Alavi, A., Rosen, M., Dann, R., Fazekas, F., Bosley, T., Greenberg, J. and Reivich, M. 1988 Cerebral metabolism and patterened visaul stimulation; a PET study of the human visual cortex. Neurology, 38 (1), 89-95, 1988.

Laavikkainen, J., Huotilainen, M., Ilmoniemi,R.J., Simola, J.T. and Naatanen, R. 1995 Pitch changes of a continuous tone activates two distinct processes in human auditory cortex: a study with whole head magnetometer. Electroencephalography and cklinical neurophysiology, 96, 93-96, 1995.
LaBerge, D. 1983 Spatial extent of attention to letters and words. J. of Experimental Psychology: Human Perception and Performance, 9, 371-379, 1983.
LaBerge, D. 1995 Attentional processing. Cambridge, MA. Harvard Uni. Press, 1995.
Lachica, E.A., Beck, P.D. and Casagrande, V.A. 1992 Parallel pathways in macaque monkey striate cortex- anatomically defined columns in layer III. Proceedings of the national Acadamy of Sciences of the USA, 89 (8), 3566-3570, 1992.
Lachica and Casagrande 1992
Lagae, L. Maes, H., Raiguel, S., Xiao, D.k and Orban, M. 1994 Responses of macaque STS neurons to optic flow components: a comparison of areas MT and MST. J. of Neurophysiology, 71, 1597-1626, 1994.
Lang, A.H., Nyrke, T., Aaltonen, Ek. M., Raimo, O. and Nätäänän, R. 1990 Pitch discrimination performance and auditive event-related potentials. In C.H.M. Brunia, A.W.K. Gaillard and A. Kok, Eds., Psychophysiological brain research, 1, 294-298. Tilburg, The Netherlands: Tilburg University Press, 1990.
Lang, A.H., Eerola, O., Korpilahti, P., Holopainen, I., Salo, S. and Aaltonen, 1995 practical issues in the clinical application of mismatch negativity. Ear and Hearing, 16, 118-130, 1995.
Lau, K.C., So, K.F., Campbell, G. and Lieberman, A.R. 1992 Pupillary constriction in response to light in rodents, which does not depend on central neural pathways. J. of the Neurological Sciences, 113, 70-79, 1992.
Lavikainen, J. 1997 Determinants of mismatch Negativity and its separation from other event-related potential componnets. Yliopistopaino, Helsinki, 1997.
Lehmann, D., Darcey, T.M. and Skrandies, W. 1982 Intracerebral and scalp fields evoked by hemiretinal checkerboard reversal and modeling of their dipole generators. In J. Courjon, F. Mauguiere and M. Revol, eds., Clinical applications of evoked potentials in neurology, pp. 41-48. New York: Raven Press. 1982.
Lennie, P., Trevarthen, C., Van essen, D. and Waessle, H. 1990. Parallel processing of visual information. In L. Spillman and J.S. Werner (Eds.), Visual Perception: the neurophysiological foundations, pp.103-128. Orlando: Academic Press, 1990.
Leuba, G. and Kraftsik, R. 1994 Visual cortex in Alzheimer's disease: occurrence of neuronal death and glial proliferation, and correlation with pathological hallmarks. Neurobiology of aging, 15, N0.1, 29043, 1994.
Levänen 1997 cited in Jääskeläinen et al 1996.
Levanthal, A,G., Rodieck, R.W. and Dreher, B. 1981 Retinal ganglion cell classes in the Old World monkey: morphology and central projections. Science, 213, 1139-1142, 1981.
Levine, D.N., Lee, J.M. and Fisher, C.M. 1993 The visual variant of Alzheimer's disease: a clinicopathologic case study. Neurology, 43, 305-313, February 1993.
Lewis, D.A., Campbell, M.J., Terry, R.D. and Morrison, J.H. 1987 Laminar and regional distribution of neurofibrillary tangles and neuritic plaques in Alzheimer's disease: a quantitative study of visual and auditory cortices. J. Neuroscience, 7, 1799-1808, 1987.
Lezak, M.D. 1995 Neuropsychological assessment (3rd ed.). Portland, OR: Oxford University Press, 1995.
Liebman, M. 1986 neuroanatomy. £rd. Ed. Aspen publishers, 1986, Maryland, USA, 1986.
Livingstone, M.S. and Hubel, D.H. 1984 Anatomy and physiology of a color system in the primate visual cortex. J. of Neuroscience, 4, 309-356, 1984.

Livingstone, M. and Hubel, D. 1988 Segregation of form, color, movement and depth: anatomy, physiology and perception. Science, 240, 740-749, 1988.
Loewy, D.h., Campbell, K.B. and Bastien, C. 1996 The Mismatch negativity to frequency deviant stimuli during natural sleep. Electroencephalography and clinical neurophysiology, 79, 281-290, 1996.
Looren De Jong, H., Kok, A., Woestenburg, J.C., Logman, C.J.C.M. and Van Rooy, J.C.G.M. 1988 Learning where to look:electrophysiological and behavioral indices of visual search in young and old subjects. Biological psychology, 26, 277-298, 1988.
Louhija,J., Miettinen, H.E. and Kontula, K. 1994 Aging and genetic variation of plasma apolipoproteins: relative loss of the apolipoprotein E4 phenotype in centenarians. Arteriosclerosis and Thromboosis, 14, 1084-1089, 1994.
Loupe, D.N., Newman, N.J., Green, R.C.m Lynn, M.J.. Williams, K.K., Geis, T.C. and Edelhauser, H.F. 1996 Pupillary response to Tropicamide in patients with Alzheimer's disease. Ophthalmology, 103, 495-503, 1996.
Lowenstein, O. and Loewenfeld, I.E. 1959 influence of retinal adaptation upon the pupillary reflex to light in normal man. Am. J. Oph. 48, 536-550, 1959.
Lowenstein, O. and Lowenfeld, I.E. 1969 The Pupil, in The Eye, Muscular Mechanisms, ed. H. Davson, Academic Press, London, pp.255-337, 1969.
Luck, S.J., Heinze, H.J., Mangun, G.R. and Hillyard, S. A. 1990 Visual event-related potentials index focused attention within bilateral stimulus arrays. II. Functional dissociation of P1 and N1 components. Electroencephalography and Clinical Neurophysiolology, 1990, 75: 528-542.
Luck, S.J. and Hillyard, S.A. 1994 (a) Electrophysiological correlates of feature analysis during visual search. Psychophysiology, 31, 1994, 291-308.
Luck, S.J., Hillyard, S.A., Mangun,G.R. and Gazzanniga, M.S. 1989 Independent attentional scanning in the separated hemispheres of split brain patients. J. of Cognitive Neuroscience, 6, 1, 84-91, 1994.
Lyytinen, H. and Naatanen, R. 1987 Autonomic and ERP responses to deviant stimuli: analysis of covariation. In R. Johnson, R. Parasuraman and J.W. Rohrbaugh (Eds.). Current trends in event-related potential research, pp. 108-117. Supplement 40 to Electroencephalography and Clinical Neurophysiology. Amsterdam: Elsevier, 1987.

Madden, D.J., Pierce, T.W., and Allen, P.A. 1996 Adult age differences in the use of distractor homogeneity during visual search. Psychology and aging, 11, (3), 454-474, 1996.
Maier, J., Dagnelie, H., Speckreise, B. and van Dijk, B.W. 1987 Principle components analysis for source localization of VEPs in man. Vision Research, 27, 165-177, 1987.
Malpeli, J.G., Schiller, P.H. and Colby, C. 1981 Response properties of single cells in monkey striate cortex during reversible inactivation of individual lateral geniculate laminae. J. of Neurophysiology, 46, 1102-1119, 1981.
Mangun, G.R. and Hillyard, S.A. 1988 Spatial gradients of visual attention: behavioural and electrophysiological evidence. Electroencephalography and Clinical Neurophsiology, 70, 417, 428, 1988.
Mangun, G.R., Hillyard, S.A. and Luck, S. J. 1993 Electrocortical substrates of visual selective attention. In Attention and Performance XIV, ed. D.E. Mayer, S. Kornblum, pp. 183-218. Cambridge, MA: MIT Press, 1993.
Mangun, G., Hopfinger, J.B., Kussmaul, C.L., Fletcher, E.M and Heinze, H-J. 1997 Covariations in ERP and PET measures of spatial selective attention in human extrastriate visual cortex. Human Brain Mapping, 5, 273-279, 1997.
Mäntysalo, S. and Naatanen, R. 1987 The duration of a neuronal trace of an auditory stimulus as indicated by event-related potentials. Biological Psychology, 24, 183-195, 1987.
Marco, L.A. 1995 Dynamic brain imaging in dementias. Abstract, p 390, Human Brain Mapping, Supplement 1, First International conference on Functional mapping of the human brain. Edited by B. Mazoyer, P. Rolan and R. Seitz, 1995.
Martin, A.J., Friston, K.J., Colebatch, J.G., Frackowiak, R.S. J. 1991 Decreases in regional cerebral blood flow with normal aging. J. of Cerebral Blood Flow Metabolism, 11, 684-689, 1991.
Martin, A., Browers, P. and Lalonde, F. 1986 Towards a behavioral typology of Alzheimer's patients. J. Clinical and Experimental Neuropsychology, 8, 594-610, 1986.
Maruff, P. and Currie, J. 1995 An attentional grasp reflex in patients with Alzheimer's disease. Neuropsychology, 33 (6), 689-701, 1995.

Maruff, P., Malone, V. and Currie, J. 1995 Asymmetries in the covert orienting of visual spatial attention to spatial and non-spatial cues in Alzheimer's disease. Brain, 118, 1421-1435, 1995.
Massman, P.J., Delis, D.C., Filoteo, J.V., Butters, N., Salmon, D.P. and Demadura, T.L. 1993 Mechanisms of spatial impairment of alzheimer's disease subgroups: differential breakdown of directed attention to global-local stimuli. Neuropsychology, 7, 172-181, 1993.
Maunsell, J.H.R. 1987 Physiological evidence for two visual subsystems. In L.M. Vaina (Ed.) Matters of intelligence, pp.59-87. Dordrecht, The Netherlands: Reidel, 1987.
Maunsell, J.H.R. and Newsome, W.T. 1987 Visual processing in monkey extrastriate cortex. Annual Review of neuroscience, 10, 363-401, 1987.
Maunsell, J.H.R. and Van Essen, D.C. 1983 The connections of the middle temporal visual area (MT) and their relationship to a cortical hierarchy in the macaque monkey. J. of neuroscience, 3, 2563-2586, 1983.
Maunsell, J.H.R., Nealey, T.A. and Depriest, D.D. 1990 Magnocellular and parvocellular contributions to responses in the middle temporal visual area ((MT) of the macaque monkey. J. of Neuroscience, 10, 3323-3334, 1990.
McCarthy, G., Spicer, M., Adrignolo,A., Luby, M., Gore, J. and Allison, T. 1995 Brain activation associated with visual motion studied by functional magnetic resonance imaging in humans. Human Brain Mapping, 2, 234-243, 1995.
McKee, A.C., Kosik, K.S. and Kowall, N.W. 1991 Neuritic pathology and dementia in Alzheimer's disease. Annals of Neurology, 30, 156-165, 1991.
McKeith, I.G. 1997 Dementia. Psychological Medicine, 27 94), 979-980, 1997.
McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D. and Stadlan, E.M. 1984 Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA work group under the auspices of department of health and human services task force on Alzheimer's disease. Neurology, 34, 939-944, July 1984.
Mendez, M.F., Mendez, M.A., Martin, R.N., Smyth, K.A. and Whitehouse, P.J. 1990(a) Complex visual disturbances in Alzheimer's disease. Neurology, 40, 439-443, 1990.
Mendez, M.F., Tomsak, R.L. and Remler, B. 1990(b) Disorders of the visual system in Alzheimer's disease. J. of Clinical Neuro-ophthalmology, 10 (1), 62-69, 1990.
Meredith, J.T. and Celesia, G.G. 1982 Pattern-reversal visual evoked potentials and retinal eccentricity. Electroencephalography and Clinical Neurophysiology, 53, 243-253, 1982.
Merigan, Byrne and Maunsell 1991. Cited in Merigan et al., 1993.
Merigan, W.H., Katz, L.M. and Maunsell, J.H.R. 1991 The effects of parvocellular lateral geniculate lesions on the acuity and contrast sensitivity of macaque monkeys. J. of Neuroscience, 11, 994-1001, 1991.
Merigan, W.H., Nealey , T.A. and Maunsell, J.H.R. 1993 Visual effects of lesions of cortical area V2 in macaques. J. Neuroscience, 13, 3180-3191, 1993.
Mesulam, M.M., Hersh, L.B., Mash, D.C. and Geula, C. 1992 Differential cholinergic innervation within functional sub-divisions of the human cerebral cortex: a choline acetylcholinesterase study. J. of Comparative Neurology, 318, 316-328, 1992.
Mesulam, M.M. and Geula, C. 1994 Chemoarchitectonics of axonal and perikaryal acetylcholinesterase along information processing systems of the human cerebral cortex. Brain Research Bulletin, 33, 137-153, 1994.
Medical Research Council Update 1996
Mendez, M.F., Mendez, M.A., Martin, R., Smyth, K.A. and Whitehouse, 1990 Complex visual disturbances in Alzheimer's disease. Neurology, 40, 439-443, 1990.
Meyer, J.S., Muramatsu, K., Mortel, K.F. 1995 Prospective CT confirms differences between vascular and Alzheimer's dementia. Stroke, 26, 735-742, 1995.
Michie, P.T., LePage, E.L., Solowij, N., Haller, M. and Terry, L. 1996 Evoked otoacoustic emissions and auditory selective attention. Hearing Research, 98, 54-67, 1996.
Micieli, G., Tassorelli, C., Martignoni, E., Pacchetti, C., Bruggi, P., Magri, M. and Nappi, G. 1991 Disordered pupil reactivity in Parkinson's disease. Clinical Autonomic Research, 1, 55-58, 1991.
Mielke, R., Kessler, J., Fink, G., Herholz, K. and Heiss, W. 1995 Dysfunction of visual cortex contributes to disturbed processing of visual information in Alzheimer's disease. Intern. J. neuroscience, 1995, Vol. 82, 1-9, 1995.
Milner, A.D. and Goodale, M.A. 1993 Visual pathways to perception and action. In 'Progress in brain research', 95, pp.317-337; ED. T.P. Hicks, S. Molotchnikoff and T. Ono. Elsevvier, Amsterdam.

Milner, A.D. and Goodale, M.A. 1997 The visual brain in action. Oxford Psychology Series No. 27, Oxford University Press, 1997.
Moran, J. and Desimone, R. 1985 Selective attention gates visual processing in the extrastriate cortex. Science, 229, 782-784, 1985.
Morecraft, R.J., Geula, C. and Mesulam, M.M. 1993 Architecture of connectivity within a cingulo-fronto-parietal neurocognitive network for directed attention. Arch. Neurology, 50, 279-284, 1993.
Moritz,D.J., Fox, P.J., Luscombe, F.A. and Kraemer, H.C. 1997 Neurological and Psychiatric predictors of mortality in patients with Alzheimer's disease. Arch. Neurol. Vol 54, 878-885, 1997.
Morrison, J.H., Scherr, S., Lewis, D.A., Campbell, M.J., Bloom, F.E., Rogers, J. and Bennet, R. 1986 the laminar and regional distribution of neocortical somatostatin and neuritic plaques: implications for Alzheimer's disease as a global disconnection syndrome. In A.B. Scheibel and A.F. Wechsler (Eds.). The biological substrates of Alzheimer's disease, pp.115-131, Orlando, FL. Academic Press, 1986.
Morrison , J.H., Hof, P.R., Campbell, M.J., DeLima, A.D., Voight, T., Bouras, C., Cox, K. and Young, W.G. 1990 Cellular pathology in Alzheimer's disease: implications for cortico-cortical disconnection and differential vulnerability. In S.I. Rapoport, H. Petit, D.Leys and Y. Christen (Eds.). Imaging, cerebral topography and Alzheimer's disease, pp.19-40, Berlin: Springer Verlag, 1990.
Motter, B.C. 1993 Focal attention produces spatially selective processing in visual cortical areas V1, V2, and V4 in the presence of competing stimuli. J. of Neurophysiology, Vol. 70, No.3, 909-919, September 1993.
Muir, J.l., Page, K.J., Sirinathsinghji, D.J.S., Robbins, T.W. and Everitt, B.J. 1993 Excitotoxic lesions of basal forebrain cholinergic neurons: effects on learning, memory and attention. behavioral Brain Research, 57, 123-131, 1993.
Muller et al 1993. Cited in Nobili and Sannita, 1997.

Naatanen, R. 1975 Selective attention and evoked potentials in humans- a critical review. Biological Psychology, 2, 237-307, 1975.
Naatanen, R., Gaillard, A.W.K. and Mäntysalo 1978 Early selective attention effect on evoked potential re-interprteed. Acta Psychologia, 42, 313-329, 1978.
Naatanen, R. 1982 Processing negativity: an evoked-potential reflection of selective attention. Psychological Bulletin, 92, 605-640, 1982.
Naatanen, R. 1984 In search of a short-duration memory trace of a stimulus in the human brain. In L. Pulkkinen and P. Lyytinen (Eds.) Human action and personality. Essays in honour of Martti Takala, pp. 29-43. Jyväskylä, 1984.
Naatanen, R. 1985 Selective attention and stimulus processing: Reflections in event-related potentials, megnetoencephalogram and regional cerebral blood flow. In M.I. Posner and O.S.M. Marin (Eds.), Attention and Performance XI, pp.355-373. Hilldale, NJ: Lawrence Erlbaun Associates, 1985.
Näätänen, R. 1986 The neural-specificity theory of visual selective attention evaluated: A commentary on Harter and Aine. Biological Psychology 23 (1986) 281-295.
Näätänen, R. 1988 Implications of ERP data for psychological theories of attention. Biological Psychology, 26, 117-163, 1988.
Näätänen, R. 1990 The role of attention in auditory information processing as revealed by event-related potentials and other brain measures of cognitive function. Behavioral and Brain Sciences, 13, 201-288, 1990.
Näätänen, R. 1991 Mismatch negativity (MMN) outside strong attentional focus: a commentary on Woldorff et al. Psychophysiology, 478-484, 1991.
Näätänen, R. 1992 Attention and Brain Function. Lawrence Erlbaum associates, Hillsdale, NJ. 1992.
Näätänen, R. 1995 The mismatch negativity: a powerful tool for neuroscience. Ear and Hearing, 16, 6-18, 1995.
Näätänen, R., Simpson, M. and Loveless, N.E. 1982 Stimulus deviance and evoked potentials. Biological psychology, 14, 53-98, 1982.
Näätänen, R., Schröger, E., Karakas, S., Tervaniemi, M. and Paavilainen, P. 1993 Development of a memory trace for a complex sound in the human brain. Neuroreport, 4, 503-506, 1993.
Näätänen,R., Paavilainen, P., Tiitinen, H., Jiang, D. and Alho, K. 1993 Attention and mismatch negativity. Psychopjhysiology, 30, 436-450, 1993.
Näätänen, R. and Alho, K. 1995 Mismatch negativity- a unique measure of sensory processing in audition. International J. of Neuroscience, 80, 317-337, 1995.

Näätänen, R. and Gaillard, A.W.K. 1983 The orienting reflex and the N2 deflection of the ERP. In A.W.K. Gaillard and W. Ritter (Eds.(, Tutorials in event-related potential research: Endogenous components, pp.119-141. Amsterdam: North Holland Publishing Company, 1983.

Näätänen, R., Gaillard, A.W.K. and Mantysalo, S. 1978 Early selective attention effect reinterpreted. Acta Psychologica, 42, 313-329, 1978.

Näätänen, R., Gaillard, A.W.K. and Mantysalo, S. 1980 Brain potential correlates of voluntary and involuntary attention. In H.H. Kornhuber and L.Deecke (Eds.), Motivation, motor and sensory processes of the brain: electrical potentials, behavior and clinical use. Progress in Brain Research, 54, pp.343-348. Amsterdam:Elsevier, 1980.

Näätänen, R., Gaillard,A.W.K. and Varey, C.A. 1981 Attention effects on auditory EPs as a function of inter-stimulus interval. Biological Psychology, 13, 173-187, 1981.

Näätänen, R. and Michie, P.T. 1979 Early selective attention effects on the evoked potential. A critical review and interpretation. Biological psychology, 8, 81-136.

Näätänen, R., Paavilainen, P., Alho, K., Reinikainen, K. and Sams, M. 1987 The mismatch negativity to intensity changes in an auditory stimulus sequence. In R. Johnson, Jr., J.W. Rohrbaugh and R. Parasuraman (Eds.) Current trends in event-related brain potential research, pp.125-131. Supplement 40, to Electroencephalography and Clinical Neurophysiology. Amsterdam: Elsevier, 1987.

Näätänen, R., Paavilainen, P., Alho, K., Reinikainen, K. and Sams, M. 1989(a) Do event-related potentials reveal the mechanism of the auditory sensory memory in the human brain ? Neuroscience Letters, 98, 217-221, 1989.

Näätänen, R., Paavilainen, P. and Reinikainen, K. 1989(b) Do event-related potentials to infrequent decrements in duration of auditory stimuli demonstrate a memory trace in man ? Neuroscience Letters, 107, 347-352, 1989.

Näätänen, R. and Picton, T. 1986 N2 and automatic versus controlled processes. In W.C. McCallum, R. Zappoli and F. Denoth (Eds.), Cerebral psychophysiology: studies in event-related potentials, EEG supplement 38, 169-172, 1986.

Näätänen, R. and Picton, T. 1987 The N1 wave of the human electric and magnetic response to sound: a review and an analysis of the component structure. Psychophysiology, 24, 375-425, 1987.

Näätänen,R., Sams, M., Järvilehto, T. and Soininen, K. 1983 cited in R.Naatanen, Attention and Brain Function, 1992. Lawrence Erlbaum Associates, Hillsdale NJ.

Näätänen,R., Simpson, M. and Loveless, N.E. 1982 Stimulus deviance and evoked potentials. Biological Psychology, 14, 53-98, 1982.

Näätänen, R., Teder, W., Alho, K. and Lavikainen 1992 Auditory attention and selective input modulation: a topographical ERP study. Neuroreport, 3, 493-496, 1992.

Nakayama, K. and Silverman, G.H. 1986 Serial and Parallel processing of visual feature conjunctions. Nature, 320, 264-265, 1986.

Nagy, Z., Esiri, M., Jobst, K., et al. 1995 Relative role of plaques and tangles in the dementia of Alzheimer's disease:correlations using three sets of neuropathological criteria. Dementia, 6, 21-31, 1995.

Nebes, R.D. and Brady, C.B. 1989 Focused and divided attention in Alzheimer's disaese. Cortex, 25, 305-315, 1989.

Neisser, U. 1967 Cognitive Psychology. New York: Appleton-Century-Crofts, 1967.

Neve, R.L., Finch, E.A., Bird, E.D. and Benowitz, L.I. 1988 Growth-associated protein GAP-43 is expressed selectively in associative regions of the human brain. Procedings of the National acadamy of Science of the the USA, 85, 3638-3642, 1988.

Neve, R.L. and Robakis, N.K. 1998 Alzheimer's disease: a re-examination of the amyloid hypothesis. TINS Vol.21, No.1, 1998.

Nissen, M.J., Corkin, S., Growdon, J., Buonanno, F.S. Growdon, J.H., Wray, S.H. and Bauer, J. 1985 Spatial vision in Alzheimer's disease: general findings and a case report. Archives of Neurology, 42, 667-671, 1985.

Noachter, S., Hashimoto, T. and Lüders, H. 1993 Pattern VEPs recorded from human occipital cortex with chropnic subdural electrodes. Electroencephalography and clinical Neurophysiology, 88, 435-446, 1993.

Nobili and Sannita 1997

Nobre, A.C., Sebestyen, G.N., Gitelman, D.R., Mesulam, M.M., Frackowiak, S.J. and Frith, C.D. 1997 Functional localization of the system for visuospatial attention using positron emission tomography. Brain (1997), 120, 515-533.

Nordby, H., Roth, W.T. and Pfefferbaum, A. 1988 (a) ? Event-related potentials to time-deviant and pitch-deviant tones. Psychophysiology, 25, 249-261, 1988.
Nordby, H., Roth, W.T. and Pfefferbaum, A. 1988 (b) Event-related potentials to breaks in sequences of alternating pitches or interstimulus intervals. Psychophysiology, 25, 262-268, 1988.
Nordby, H., Hammerborg, D., Roth, W.T. and Hugdahl, K. 1991 ERPs to infrequent omissions and inclusions of stimulus elements. Psychophysiology, 28, S42, 1991.
Norman and Werblin 1974
Nothdurft, H.C. 1991 Texture segmentation and pop-out from orientation contrast. Vision Research, 31, 1073-1078, 1991.
Nothdurft, H.C. 1993 The role of features in preattentive vision: comparison of orientation, motion and colour cues. Vision Research, 33, 1937-1958, 1993.
Nothdurft, H.C. 1995 Generalized feature contrast in preattentive vision. Perception, 24, 22, 1995.,
Novak, G., Ritter, W., Vaughan, H.G. and Wiznitzer, M.L. 1990 Differentiation of negative event-related potentials in an auditory discrimination task. Electroencephalography and Clinical Neurophysiology, 75, 255-275, 1990.
Nyman, G., Alho, K., Laurinen, P., Paavilainen,P., radil, T., Reinikainen, K., Sams, M. and Naatanen, R. 1990 Mismatch negativity (MMN) for sequences of auditory and visual stimuli: evidence for a mechanism specific to the auditory modality. Electroencephalography and Clinical Neurophysiology, 77, 436-444, 1990.

O'Brien, J.T., Eagger, S., Syed, G.M.S., Sahakian, B.J. and Levy. 1992 A study of regional uptake decrease and cognitive performance in Alzheimer's disease. J. of Neurology, Neurosurgery and Psychiatry, 55, 1182—1187, 1992.
O'Craven, K.M., Rosen, B.R., Kwong, K.K., Treisman, A. and Savoy, R.L. 1997 Voluntary attention modulates fMRI activity in human MT-MST. Neuron, 18, 591-598, 1997.
Oken, B.S., Kishiyama, S.S. and Kaye, J.A. 1994 Age-related differences in visual search task performance: relative stability of parallel but not serial search. J. of Geriatric psychiatry and Neurology, 7, 163-168, 1994.
Oken, B.S., Kishiyama, S.S., Kaye, J.A., and Howieson, D.B. 1994 Attention deficit in Alzheimer's disease is not simulated by an anticholinergic/ antihistaminergic drug and is distinct from deficits in healthy aging. Neurology, 44, 657-662, 1994.
Olvarria, Knierim, Fox, Sagi and Julesz 1989
O'Neil, D. 1991 Carers, professionals and alzheimer's disease. John Libbey, London, 1991.
Onofrj, M., fulgente, T., Maloctresta, G., Ferracci, F. 1993 VEPs to altitudinal stimuli: effects of stimulus manipulation on VEP scalp topography. Clinical Vision Science, 8, 529-544, 1993.
Orwin, A., Wright, C.E., Hording, G.F.A., Rowan, D.C. and Rolfe, E.B. 1986 Serial visual evoked potential recordings in Alzheimer's disease. British Medical Journal, 293, 9-10, 1986.
Ostereicher et al 1988
O'Toole, A.J. and Walker, C.L. 1997 On the preattentive accessibility of stereoscopic disparity: evidence from visual search. Perception and Psychophysics 59 (2), 202-218, 1997.

Paavilainen, P., Camman, R., Alho, K., Reinikainen, K., Sams, M. and Näätänen, R. 1987 Brain responses to pitch changes in repetitive tone sequences during sleep. In R. Johnson, Jr., R. Parasuraman and J.W. Rohrbaugh (Eds.), Current trends in event-related potential research (pp246-255). Amsterdam:Elsevier, 1987.
Paavilainen, P., Alho, K., Reinikainen,K., Sams, M. and Näätänen, R. 1991 Right hemisphere dominance of different mismatch negativities. Electroencephalography and Clinical Neurophysiology, 78, 466-479, 1991.
Paavilainen, P., Tiitinen, H., Alho, K. and Näätänen, R. 1993, mismatch negativity to slight pitch changes outside strong attentional focus. Biological Psychology, 37, 23-41, 1993.
Paavilainen, P., Saarinen, J., Tervaniemi, M. and Naatanen, R. 1995 Mismatch Negativity to changes in abstarct sound features during dichotic listening. J. of Psychophysiology, 9, 243-249, 1995.
Parasuraman,R., Greenwood, P.M., Haxby, J.V. and Grady, C.L. 1992 Visuospatial attention in dementia of the Aklheimer type. Brain, 115, 711-733, 1992. (? a and b)
Partanen, J., Hartikainen, P., Könönen,M., Jousmäki, V., Soininen, H., and Reikkinen, P., Sr. 1994 Prolonged latencies of pattern reversal visual evoked early potentials in Alzheimer's disease. Alzheimer's Disease and Associated Disorders, 8 (4), 250-258.

Patten, J. 1982 Neurological Differential Diagnosis. H. Stark Ltd. London, chapter 2, 'The pupils and their reactions'.1982.
Pearlman, A.L., Birch, J. and Meadows, J.C. 1979 Cerebral color blindness:an acquired defect in hue discrimination. Annals of Neurology, 5, 253-261, 1979.
Pearson 1996
Pearson, R.C.A., Esiri, M.M., Hiorns, R.W., Wilcock, G.K. and Powell, T.P.S. 1985 Anatomical correlates of the distribution of the pathological changes in the neocortex in Alzheimer's disease. Proceedings of the National Academy of Science, 82, 4531-4534, 1985.
Pekkonen 1995
Pekkonen, E., Jousmäki, V., Partanen, J. and Karhu, J. 1993 Mismatch negativity area and age-related auditory memory. Electroencephalography and Clinical neurophysiology, 87, 321-325, 1993.
Pekkonen, E., Jousmäki, V., Könönen, M., Reinikainen, K. and Partanen, J. 1994 Auditory sensory memory impairment in Alzheimer's disease: an event-related potential study. NeuroReport, 5, 2537-2540, 1994.
Pekkonen, E., Jousmäki, V., Reinikainen, K. and Partanen, J. 1995(a) Automatic auditory discrimination is impaired in Parkinson's disease. Electroencephalography and Clinical Neurophysiology, 95, 47-52, 1995.
Pekkonen, E., Rinne, T. and Naatanen, R. 1995(b) Variability and replicability of the mismatch negativity. Electroencephalography and clinical neurophysiology, 96, 546-554, 1995.
Peppard, Martin, Carr, Grochowski, Schulzer, Guttman, McGeer, Phillips, Tsui and Calne 1992
Perenin, M.T. and Jeannerod, M. 1978 Visual function within the hemiannopic field following early cerebral hemidecortication in man: 1. Spatial localisation. Neurppsychologia, 16, 1-13, 1978.
Phillips, W.A. 1983 Short-term visual memory. Phi. Trans. Of the Royal society, London, B., 302: 295-309, 1983.
Philips, D.P. and Orman, S.S. 1984 Responses of single neurons in posterior field of cat auditory cortex, to tonal stimulation. J. of Neurophysiology, 51, 147-163, 1984.
Phillips, D.P., Orman,S.S., Musicant, A.D. and Wilson, G.F. 1985 Neurons in the cat's primary auditory cortex distinguished by their responses to tones and wide-spectrum noise. Hearing research, 18, 73-86, 1985.
Philpot, M.P., Amin, D. and Levy, R. 1990 Visual evoked potentials in Alzheimer's disease: correlations with age and severity. Electroencephalography and clinical Neurophysiology, 77, 323-329, 1990.
Picton, T. 1992 The P300 wave of the human event-related potential. J. of Clinical Neurophysiology, 9 (4): 456-479.
Plude, D.J. and Doussard-Roosevelt, J.A. 1989 Aging, selective attention and feature integration. Psychology and Aging, 4, 98-105, 1989.
Pomara, N. and Sitaram, N. 1995 Detecting Alzheimer's disease [letter]. Science, 267 (5204), 1579-81, 1995.
Pöppel, E., Held, R. and Frost, D. 1973 Residual visual function after brain wounds involving the central visual pathways in man. Nature, 243, 295-296, 1973.
Posner, M.I. 1980 Orienting of attention. Quarterly J. of Experimental Psychology, 32, 3-25, 1980.
Posner, M.I., Walker, J.A., Friedrich, F.J. and Rafal, R.D. 1984 Effects of parietal injury on covert orienting of attention. J. Neuroscience, 4, 1863-1974.
Posner, M.I. and Cohen, Y. 1984 Components of visual orienting. In H. Bouma and D.G. Bouwhuis (Eds.), Attention and Performance, vol, 10, pp.531-556. Hillsdale, NJ: Erlbaum, 1984.
Posner, M.I. and Dehaene, S. 1994 Attentional networks. TINS, Vol.17, No.2, 1994.
Posner, M.I., Werner-Inhoff, A., Freidrich, F.J. and Coshen, A. 1987 Isolating attentional systems: a cognitive-anatomical analysis. Psychobiology, 15, 2, 107-121, 1987.
Potter, H. 1991 Review and Hypothesis: Alzheimer's disease and Down syndrome-chromasome 21 nondisjunction may underlie both disirders. American J. of Human Genetics, 48, 1192-1200, 1991.
Prechtl, J.C. and Bullock, T.H. 1993 Plurality of visual mismatch potentials in a reptile. J. of Cognitive Neuroscience 5:2, 177-187, 1993.
Previc, F.H. and Harter, M.F. 1982 Electrophysiological and behavioral indicants of selective attention to multifeature gratings. Perception and Psychophysics, 32, 465-472.
Pulvermüller, F. 1996 Hebb's concept of cell assemblies and the psychophysiology of word processing. Psychophysiology, 33, 317-333, 1996.

Ramachandran, V.S. 1988 Perception of shape from shading. Nature, 331, 163-166, 1988.
Rappaport, S.I., Howitz, B., Grady, C.L., Haxby, J.V., DeCarli, C. and Shapiro, M.B. 1991 abnormal brain metabolism in Alzheimer's disease, as measured by positron emission tomography. In M. Vranic (Ed.), Fuel homeostasis and the nervous system, pp.231-248, 1991.
Raskind, M.A., Sadowsky, C.H., Sigmund, W.R., Beitler, P.J. and Auster, S.B. 1997 Effect of Tacrine on language, praxis, and noncognitive behavioral problems in Alzheimer's disease. Arch Neurol., Vol. 54, 836-840, 1997.
Ray, P.G., Meador, K.J., Loring, D.W., Murro, A.M., Buccafusco, J.J., Yang, X-H., Zamrini, E.Y., Thompson, W.O. and Thompson, E.E. 1991 Effects of scopolamine on visual evoked potentials in aging and dementia. Electroencephalography and clinical Neurophysiology, 80, 347-351, 1991.
Raz, N. 1996 neuroanatomy of the aging brain: evidence from structural MRI. In Neuroimaging II: clinical applications. Ed. E.D. Bigler. New York Plenum Press, 1996.
Raz, N., Gunning, F.M., Head, D., Dupuis, J.H., McQuain, J., Briggs, S.D., Loken, W.J., Thornton, A.E., and Acker, J.D. 1997 Selective aging of the human cerebral cortex observed in vivo: differential vulnerability of the prefrontal gray matter. Cerebral cortex, 268-282; 1047-3211, Apr/May, 1997.
Regan, D. and Neima, D. 1984 Low-contrast letter charts in early diabetic retinopathy ocular hypertension, glaucoma and Parkinson's disease. British J. of Ophthalmology, 68, 885-889, 1984.
Reitner, A., Baumgartner, I., Thuile, C., Dilmaghani, R.B., Ergun. E., Kaminski, S., Lukas, J. and Dal Bianco, P. 1997 The mydriatic effect of tropicamide and its diagnostic use in Alzheimer's disease. Vision Research, 37, 1, 165-168, 1997.
Renault, B., Ragot, R., Lesèvre, N., and Remond, A. 1982 Onset and offset of brain events as indices of mental chronometry.
Ritter, W. Paavilainen, P., Lavikainen, J., Reinikainen, J., Alho, K., Sams, M. and Naatanen, R. 1992 Event-related potentials to repetition and change of auditory stimuli. Electroencephalography and clinical Neurophysiology, 83, 306-321, 1992.
Ritter, W., Vaughan, H.G., Jr. And Simson, R. 1983 On relating event-related potential components to stages of processing. In A.W.K. Gaillard and W. Ritter (Eds.) Tutorials in event-related potential research: Endogenous components, pp. 143-158. Amsterdam: North Holland Publishing Company. 1983.
Ritter, W. and Ruchin, D.S. 1992 A review of event-related potential components discovered in the context of studying P3. Annals of the New York academy of Sciences, 658, 1-32, 1992.
Ritter, W., Deacon, D., Gomes, H., Javitt, D.C. and Vaughan, H.G. 1995 The mismatch negativity of event related potentials as a probe of transient auditory memory: A review. Ear and Hearing, 16, 52-67, 1995.
Rizzo, J.F., Cronin-Golomb, A., Growdon. J.H., Corkin, S., Rosen. T.J., Sandberg, M.A., Chiappa, K.H. and Lessell, S. 1992 Retinocalcerine function in Alzheimer's disease. Arch. Neurol., Vol 49, 93-101, January 1992.
Rockland, K.s. and Van Hoesen, G.W. 1994 direct temporal-occipital feedback connections to straite cortex (V1) in the macaque monkey. Cerebral Cortex, 4, 300-313, 1994.
Roth, G.S., Joseph, J.A. and Mason, R.P. 1995 Membrane alterations as causes of impaired signal transduction in Alzheimer's disease and aging. TIND, Vol. 18, No.5, 203-205, 1995.
Ruessmann, K. and Beneicke, U. 1991 P2 latency of the flash visual evoked potential in dementia. Intern. J. Neuroscience, 1991, Vol.56, 273-276, 1991.
Rugg ref. P4
Rugg, M.D., Milner, A.D., Lines, C.R. and Phalp, R. 1987 Modulation of visual event-related potentials by spatial and non-spatial visual selective attention. Neuropsychologia, 25, 85-96, 1987.

Sacks, B. and Smith, S. 1989 People with Down's syndrome can be distinguished on the basis of cholinergic dysfunction. J. of Neurology, Neurosurgery and Psychiatry, 52, 1294-1295, 1989.
Sadun, A.A., Borchert, M., De Vita, E., Hinton, D.R. and Bassi, C.J. 1987 Assessmsnt of visual impairment in patients with Alzheimer's disease. American J. of Ophthalmology, 104, 113-120, 1987.
Sahakian, B.J., Sownes, J.J., and Eagger, S. 1990 sparing of attentional relative to mnemonic function in a subgroup of patients with dementia of the Alzheimer's type. Neuropsychologia, 11, 1197-1213, 1990.
Sagi, D. and Julesz, B. 1984 Detection versus discrimination of visual orientation. Perception 13, 619-628, 1984.

Sallinen, M. and Lyytinen, H. 1997 Mismatch negativity during objective and subjective sleepiness. Psychophysiology, 34, 694-702, 1997.
Sams, M., Alho, K. and Naatanen, R. 1983 sequential effects in the ERP in discriminating two stimuli. Biological Psychology, 17, 41-58, 1983.
Sams, M., Alho, K. and Naatanen, R. 1984 Short-term habituation and dishabituation of the mismatch negativity of the ERP. Psychophysiology, 21, 434-441, 1984.
Sams, M., Hamalainen, M., Antervo, A., Kaukoranta, E., Reinikainen, K. and Hari, R. 1985 Cerebral neuromagnetic responses evoked by short auditory stimuli. Electroencephalography and Clinical Neurophysiology, 61, 254-266.
Sams, M., Paavilainen, P., Alho, K. and Naatanen, R. 1985 (b) Auditory frequency discrimination and event-related potentials. Neuroencephalography and Clinical Neurophysiology, 62, 437-448, 1985.
Sams,M., Aulanko, R., Aaltonen, O. and Näätänen, R. 1990 Event-related potentials to infrequent changes in synthesized phonetic stimuli. J. of Cognitive Neuroscience, 2, 344-357, 1990.
Sams, M., Kaukoranta, E., Hämäläinen, M. and Näätänen, R. 1991 Cortical activity elicited by changes in auditory stimuli:different sources for magnetic N100 m and mismatch responses. Psychophysiology, 28, 21-29, 1991.
Sams, M., Paavilainen, P., Alho, K. and Naatanen, R. 1985 Auditory frequency discrimination and event-related potentials. Electroencephalography and Clinical Neurophysiology, 62, 437-448, 1985.
Sams, M., Hari, R., Rif, J. and Knuutila, J. 1993 The human auiditory sensory memory trace persists about 10 sec: Neuromagnetic evidence. J. of Cognitive Neuroscience, 5, 363-370, 1993.
Schein, S.J. and Desimone, R.J. 1990 cited in F. crick and C. Koch; are we aware of neural activity in primary visual cortex ?. Nature, 375, 121-123, 1995.
Scherg, M., Vajsar, J. and Picton, T. 1989 A source analysis of the human auditory evoked potentials. J. Cognitive Neuroscience, 1, 336-355, 1989.
Shiffrin, R.M., 1975 The locus and role of attention in memory systems. In P.M.A. Rabbitt and S. Dornic (Eds.), Attention and Performance V, pp. 168-193, London: Academic Press, 1975.
Schiller, P.H., 1996 On the specificity of neurons in visual areas. Behavioural Brain Research, vol. 26, No. 1-2, pp 21-35, 1996.
Schiller, P.H., Logothetis, N.K. and Charles, E.R. 1990 Role of the color opponent and broad band channnels in vision. Visual neuroscience, 5, 321-346, 1990.
Schiller, P.H. and Logothetis, N.K. 1990 The color-opponent and broad-band channels of the primate visual system. TINS, Vol. 13, No. 10, 1990.
Schiller, P.H., Logothetis, N.K. and Charles, E.R. 1990 Functions of the color-opponent and broad-band channels of the visual system. Nature, 343, 68-70, 1990.
Schlotterer, G., Moscovitch, M. and Crapper-McLachlan, D. 1983 Visual processing deficits as assessed by spatial frequency contrast sensitivity and backward masking in normal aging and Alzheimer's disease. Brain, 107, 309-325, 1983.
Schneider, W. and Shiffrin, R.M. 1977 Controlled and automatic human information processing: I. Detection, search, and attention. Psychological Review, Vol. 84, No. 1, January 1977.
Schreiner, C.E., Mendelson, J.R. and Sutter, M.L. 1992 Functional topography of cat primary auditory cortex: representation of the tone intensity. Experimental Brain Research, 92, 105-122, 1992.
Schröger, E., Naatanen, R. and Paavilainen, P. 1992 Event-related potentials reveal how non-attended complex sound patterns are represented by the human brain. Neuroscience Letters, 146, 183-186, 1992.
Scinto, L.F., Daffner, K.R., Dressler, D., Ransil, B.I., Rentz, D., Weintraub, S., Mesulam, M. and Potter, H. 1994 A potential non-invasive neurobiological test for Alzheimer's disease. Science, 266 (5187), 1051-1054, 1994.
Shiffrin, R.M. and Schneider, W. 1977 Controlled and automatic information processing: II. Perceptual learning, automatic attending, and a general theory. Psychological Review, Vol. 84, No. 2, March 1977.
Seeck, M., Schomer, D., Mainwaring, N., Ives, J., Dubuisson, D., Blume, H., Cosgrove, R., Ransil, B.J. and Mesulam, M.-M. 1995 Selectively distributed processing of visual object recognition in the temporal and frontal lobes of the human brain. Ann. Neurol. 37, 538-545, 1995.
Sejnowski, T.R. 1986 Open questions about computation in cerebral cortex, In Parallel distributed processing, vol.2: Psychological and biological models. J.L. McClelland and D.E. Rumelhart, Eds, pp. 372-389. Cambridge, MA: MIT Press, 1986.

Seki, K., Nakasato, N., Fujita, S., Hatanaka, K., Kawamura, T., Kanno. And Yoshimoto, T. 1996 Neuromagnetic evidence that the P100 component of the pattren reversal visual evoked response originates in the bottom of the calcarine fissure. Electroencephalography and clinical Neurophysiolgy, 100, 436-442, 1996.

Selkoe, D.J. 1996 cited in Neve and Robakis, 1998.

Shelley, A.M., Ward, P.B., Michie, P.T., Andrews, S., Catts, S.V. and Mc Conaghy, N. 1991 The effect of repeated testing on ERP components during auditory selective attention. psychophysiology, 28, 496-510, 1991.

Shröger, E. and Winkler, I. 1995 Presentation rate and magnitude stimulus deviance effects on human pre-attentive change detection. Neuroscience Letters, 193, 185-188, 1995.

Shröger, E. 1994 Automatic detection of frequency change is invariant over a large intensity range. Neuroreport, 5, 825-828, 1994.

Shröger, E. 1996 The influence of stimulus intensity and inter-stimulus interval on the detection of pitch and loudness changes. Electroencephalography and clinical Neurophysiology, 100, 517-526, 1996.

Shröger, E. 1997 On the detection of auditory deviations: a pre-attentive activation model. Psychophysiology, 34, 245-257, 1997.

Silverman,S.E., Tran, D.B., Zimmerman, K.M. and Feldon, S.E. 1994 Dissociation between the detection and perception of motion in Alzheimer's disease. Neurology 44, 1814-1818, 1994.

Simson, R., Vaughan, H.G. and Ritter, W. 1977 The scalp potentials in auditory and visual discrimination tasks. Electroencephalography and clinical Neurophysiology, 42, 528-535, 1977.

Singer, W. and Gray, C.M. 1995 Visual feature integration and the temporal correlation hypothesis. Annual Review of Neuroscience, 18, 555-586.

Sinkkonen, J., Kaski, S., Huotilainem, M., Ilmonniemi,R.J., Naatanen, R. and Kaila, K. 1996 Optimal resource allocation for novelty detection in a human auditory memory. Neuroreport, 7, 2479-2482, 1996.

Skrandies, W. 1995 visual information processing: topography of brain electrical activity. Biological Psychology 40, 1995, 1-15.

Slamovits, T.L. and Glaser, J.S. 1995 The pupila and accommodation. In Duane's clinical Ophthalmology, Vol.". W.Tasman and E.A. Jaeger eds. Lippincott-Rowen, 1995.

Sloan, E.P. and Fenton, G.W. 1992 Serial visual evoked potential recordings in geriatric psychiatry. Electroencephalography and clinical Neurophysiology, 84, 325-331, 1992.

Slooter, J. and van Noren, D. 1980 Visual acuity measured with pupil responses to checkerboard stimuli. Investigative Ophthalmology and Visual Science, 19, 105-108, 1980.

Smith, S.A. 1992 Pupil Function: tests and disorders. In Autonomic Failure, 3rd Edition. Edited R.Bannister and C.J. Mathias. Oxford University Press, Oxford, 1992.

Smith, S.A. and Dewhirst, R.R. 1986 A simple diagnostic test for pupillary abnormality in diabetic autonomic neuropathy. Diabetic Medicine, 3, 38-41, 1986.

Smith, S.A. and SmithS.E. 1983 Reduced pupillary light reflexes in diabetic autonomic neuropathy. Diabetologia, 24, 330-332, 1983.

Smith, S.E., Smith, S.A., Brown, P.M., Fox, C. and Sonksen, P.H. 1978 Pupillary signs in diabetic autonomic neuropathy. British Medical Journal, 2, 924-927, 1978.

Smith, V.C., Lee, B.B., Pokorny, J., Martin, P.R. and Valberg, A. 1992 Responses of macaque ganglion cells to the relative phase of heterochromatic modulated lights. J. of Physiology, 458, 191-221, 1992.

Smith, Sayre, Monnier and Perry 1995 cited in Neve and Robakis, 1998.

Snyder, E.W., Dustman, R.E. and Shearer, D.E. 1981 Pattern reversal evoked potential amplitude: life span changes. Electroencephalography and clinical neurophysiology, 52, 429-434, 1981.

Sorenson, E.M., Parkinson, D., Dahl, J.L. and Chiappinelli, V.A. 1989 Immunohistochemical localization of choline acetyltransferase in the chicken mesencephalon. J. of Comparative Neurology, 281 (4), 641-657, Mar. 22., 1989.

Sperling, G. 1960 The information available in brief visual presentations. Psychol. Monogr. 74, 11, whole of No. 498, 1960.

Spitzer, H. and Richmond, B.J. 1991 Task difficulty: Ignoring, attending to, and discriminating a visual stimulus yield progressively more activity in inferior temporal neurons. Exp. Brain Res., 83: 340-348.

Squires, N.K., Squires, K.C. and Hillyard, S.A. 1975 Two varieties of long-latency positive waves evoked by unpredictable auditory stimuli in man. Electroencephalography and Clinical Neurophysiology, 38, 387-401, 1975.
Stam, V.J., Visser, S.L., Op de Coul, A.A., De Sonneville, L.M.J., Schellens, R.L.L.A., Brunia, C.H.M., de Smet, J.S. and Gielen, G. 1993 Distrurbed frontal regulation of attention in Parkinson's disease. Brain, 116, 1139-1158, 1993.
Steinman, B.A., Steinman, S.B. and Lehmkuhle, S. 1997 Transient visual attention is dominated by the magnocellular stream. Vision Research, 37, 17-23, 1997.
Steinschneider ref B15
Straub, R.H., Thies, U. and Kerp, L. 1992 The pupillary light reflex. 1. Age-dependent and age-independent parameters in normal subjects. Ophthalmological, 204, 134-142, 1992.
Stroop, J. 1935 Studies of interference in serial verbal reactions. J. of Experimental Psychology, 18, 643-661.
Sulkava, R., Kainulainen, K., Verkkoniemi, A., Niinistö, L., Sobel, E., Davanipour, Z., Polvikoski, T., Halta, M. and Kontula, K. 1996. APOE alleles in Alzheimer's disease and vascular dementia in a population aged 85+. Neurobiology of aging, 17, N0. 3. 373-376, 1996.
Sullivan, M., Faust, M.E. and Balota, D.A. 1995 Identity negative priming in older adults and individuals with dementia of the Alzheimer type. Neuropsychology, 9, 537-555.
Swanwick,G.R.J., Rowan, M., Coen, R.F., O'Mahony, D., Lee, H., Lawlor B.A., Walsh, J.B. and Coakley, D. 1996 clinical application of electrophysiological markers in the differential diagnosis of depression and very mild Alzheimer's disease. J. of Neurology, Neurosurgery, and Psychiatry 1996; 60: 82-86.

Tanaka, K., Hikosaki, K., Saito, H., Yukie, M., Fukada, Y. and Iwai, E. 1986 Analysis of local and wide-field movements in the superior temporal visual areas of the macaque monkey. J. Neuroscience, 6, 134-144, 1986.
Tanaka, K. 1993 Neuronal mechanisms of object recognition. Science, Vol. 62, 29 October 1993.
Tedeschi, G., Bertolino, A., Lundbom, N., Bonavita, S., Patronas, N.J., Duyn, J.H., Verhagen Metman, L., Chase, T.N. and Di Chiro, G. 1996 Cortical and subcortical chemical pathology in Alzheimer's disease as assessed by multislice propton magnetic resonance spectroscopic imaging. Neurology 47, 696-704, 1996.
Teder, W. K., Alho, K., Reinikainen, K. and Näätänen, R. 1993 Interstimulus interval and the selective-attention effect on auditory ERPs: N1 enhancement versus processing negativity. Psychophysiology, 30, 71-81, 1993.
Tervaniemi, M., Alho, K., Paavilainen, P., Sams, M. and Naatanen, R. 1993 Absolute pitch and event-related brain potentials. Music Perception, 10, 3, 305-316, Spring, 1993.
Theeuwes, J. 1994 stimulus-driven capture and attentional set: selective search for colour and visual abrupt onsets. J. of Experimental Psychology: Human Perception and Performance, 20, (4), 799-806, 1994.
Thorell, L.G., DeValois, R.L. and Albrecht, D.G. 1984 Spatial mapping of monkey V1 cells with pure color and luminance stimuli. Vision Research, 24, 751-769, 1984.
Tien, R., Felsberg, G., Ferris, N. and Osumi, A. 1993 The dementias: correlation of clinical features, pathophysiology and neuroradiology. American J. of Roentgenology, 161, 245-255, 1993.
Tiitinen, H, Alho, K., Huotilainen, M., Ilmoniemi, R.J., Simola, J. and Naatanen, R. 1993 Tonotopic auditory cortex and the magnetoencephalographic (MEG) equivalent of the mismatch negativity. Psychophysiology, 30, 537-540, 1993.
Timsit-Berthier, M., Mantanus, H. and Legros, J.J. 1983 EEG-reactivity and event-related potential approach to the study of vasop[ressin. In E. Endroeczi, L. Angelucci, D. DeWied, and U. Scapagnini (Eds.) Neuropeptides and Psychosomatic Processes, pp.63-71. Buda-pest, Hungary: Academiai Kiado, 1983.
Tobimatsu, S., Kurita-Tashima, S., Nakayama-Hiromatsu, M., Akazawa, K. and Kato, M. 1993 Age-related changes in pattern visual evoked potentials: differential effects of luminance, contrast and check size. Electroencephalography and clinical Neurophysiology, 88, 12-19, 1993.
Tobimatsu, S., Hamada, T., Okayama, M., Fukui, R. and Kato, M. 1994 Temporal frequency deficit in patients with senile dementia of the Alzheimer's type: a visual evoked potential study. Neurology, 44, 1260-1263, 1994.

Tootell, R.B.H., Reppaas, J.B., Dale, A.M., Look, R.B., Sereno, M.I., Malach, R., Brady, T.J. and Rosen, B.R. 1995 Visual motion aftereddect in human cortical area MT revealed by functional magnetic resonance imaging. Nature, 375, 139-141, 1995.
Tootell, R.B.H., Dale, A.M., Sereno, M.I. and Malach, R. 1996 New images from human visual cortex. TINS, 19, (11), 481-489, 1996.
Tovée, M.J. 1996 An introduction to the visual system. Cambridge University Press, 1996
Treisman, A. 1982 Perceptual grouping and attention in visual search for features and for objects. J. of Experimental Psychology: Human Perception and Performance, 8, 194-214, 1982.
Treisman, A.M. 1985 Preattentive processing in vision. Computer Vision, Graphics and Image Processing, 31, 156-177, 1985.
Treisman, A. 1988 Features and objects: The Fouteenth Bartlett Memorial Lecture. Quarterly J. of Experimental Psychology, 40A, 201-237, 1988.
Treisman, A.M. 1986 Features and objects in visual processing. Scientific american, 254, 114-124, 1986.
Treisman, A. 1991 Search, similarity and integration of features between and within dimensions. J. of Experimental Psychology: Human Perception and Performance, 17, 652-676, 1991.
Treisman, A. 1996 The binding problem. Current opinion in Neurobiology, 6, 171-178, 1996.
Treisman, A.M. and Gelade, G. 1980 A feature integration theory of attention. Cognitive Psychology, 12, 97-136, 1980.
Treisman, A.M. and Gormican, S. 1988 Feature analysis in early vision: evidence from search asymmetries. Psychological Review, 95, 15-48.
Treisman, Gormican and Cohen 1993
Treisman, A.M. and Sato, S. 1990 Conjunction search revisited. J. Exp. Psychology, 16, 459-478, 1990.
Treisman, A.M, Sykes, M. and Gelade, G. 1977 Selective attention and stimulus integration, in Attention and Performance, VI Ed., S.Dornic, pp.333-361. Hillsdale, NJ. Lawrence Erlbaum Associates, 1977.
Treue, S. and Maunsell, J.H.R. 1996 Attentional modulation of visual motion processing in cortical areas MT and MST. Nature, Vol. 382, 8 august 1996, 539-541.
Treolar, A., Assin, M. and Macdonald, A. 1996. Pupillary response to topical tropicamide as a marker for Alzheimer's disease. British J. of Clinical Pharmacology, 41, 256-257, 1996.
Trick, G.L., Barris, M.C. and Bickler-Bluth, M. 1989 Abnormal pattern electroretinograms in patients with senile dementia of the Alzheimer's type. Annals of Neurology, 26, 226-231, 1989.
Trick, L.M. and Enns, J.T. 1997 Measuring preatentive processes: when is pop-out not enough ? Visual cognition, 4 (2), 163-198, 1997.
Troscianko, T. and Calvert, J. 1993 Impaired parallel visual search mechanisms in Parkinson's disease: implications for the role of dopamine in visual attention. clinical Vision Science, 8, 3, 281-287., 1993.
Troscianko, T., Davidoff, J., Humphreys, G., Landis, T., Fahle, M., Greenlee, M., Brugger, P. and Phillips, W. 1996 Human colour discrimination based on a non-parvocellular pathway. Current Biology, Vol. 6 No. 2:200-210, 1996.
T'so, D.Y. and Gilbert, C.D. 1988 The organization of chromatic and spatial interactions in the primate striate cortex. J. of Neuroscience, 8, 1712-1727, 1988.
Turner, J.D. 1994 GABAergic systems and dementia. In D. Nicholson (Ed.) Anti-dementia agents, pp. 252-271, Academic Press Ltd., 1994

Ukai, K. 1985 Spatial pattern as stimulus to the pupillary system. J. of the optical Society of America, 2, 1094-1100, 1985.
Ullsperger, P. and Baldeweg, T. 1990 Sensory adaptation and mismatch negativity, pp. 255-256, in Naatanen, 1990.
Ungerleider, L.G. and Mishkin, M. 1982 Two cortical visual systems. In Analysis of Visual Behavior, ed. J. Ingle, M.A. Goodale, R.J.W. Mansfield, pp. 549-586, 1982.
Ungerleider, L.G. and Haxby, J. 1994 What and where in the human brain. Curr. Opin. Neurobiol. 4, 157-165, 1994.

Van Essen, D.C., Anderson, C.H. and Felleman, D.J. 1992 information processing in the primate visual system: an integrated systems perspective. Science, 255, 419-423, 1992.

Van Essen, D.C. and De Yoe, E.A. 1995 Concurrent processing in the primate visual system. In The Cognitive neurosciences, M.S. Gazzaniga (Ed.), pp.383-400, 1995.
Vaughan, H.G. 1966 The perceptual and physiologic significance of vocal evoked resposnes recorded from the scalp in man. In H.M. Burian and J.H. Jacobson (eds.), Clinical electro-retinography: Proceedings of the 3rd International symposium. Pergamon Press, Oxford, 1966.
Vaughan, H,G. and Arezzo, J.C. 1992 The neural basis of ERPs. In T.W. Picton (ed.), Human ERPs. Handbook of electroencephalography and clinical neurophysiology (revised series, vol. 3), pp. 45-96> Elsevier, Amsterdam, 1992.
Verkhratsky, A. and Toescu, E.C. 1998 calcium and neuronal ageing. TINS Vol.21, No.1, 1988
Verleger, R., Kömpf, D. and Neukäter, W. 1992 Event-related EEG potentials in mild dementia of the Alzheimer type. Electroencephalography and Clinical Neurophysiology, 84, 332-343, 1992.
Von der Malsburg, C. 1995 Binding in models of Perception and brain function. Current opinion in Neurobiology, 5, 520-526, 1995.

Wade and Roush 1997. Cited in Neve and Robakis, 1998.
Waldemar, G. 1995 Functional brain imaging with SPECT in normal aging and dementia: methodological, pathophysiological and diagnostic aspect. Cerebrovascular Brain Metabolism Review, 7, 89-130, 1995.
Wang, Q., Cavanagh, P. and Green, M. 1994 Familiarity and pop-out in visual search. Perception and Psychophysics, 1994, 56, 5, 495-500.
Watson, D.G. and Humphreys, G.W. 1997 Visual Marking: Prioritizing selection for new objects by Top-Down attentional inhibition of old objects. Psychological review, 1997, 104, 1, 90-122.
Weinstein, A., Troscianko, T. and Calvert, J. 1997 Impaired visual search mechanisms in Parkinson's disease (PD): a psychophysical and event-related potentials study. J. of Psychophysiology, 11, 33-47, 1997.
Weiskrantz, L., Warrington, E.K., Sanders, M.D. and Marshall, J. 1974 Visual capacity in the hemianopic field following a restricted occipital ablation. Brain, 97, 709-728, 1974.
Whittaker and Siegfried 1983
Wijers, A.A., Okita, T., Mulder, G., Mulder, L.J.M., Lorist, M.M., Poiesz, R. and Scheffers, M.K. 1987 Visual search and spatial attention: ERPs in focused and divided attention conditions. Biological Psychology, 25, 33-60, 1987.
Wijers, A.A., Mulder, G., Okita, T., Mulder, L.J. and Scheffers, M.K. 1989 (a) Attention to color: an analysis of selection, controlled search, and motor activation, using event-related potentials. Psychophysiology, 26, 89-109.
Wilcock, G.K. and Esiri, M.M. 1982 Plaques, tangles and dementia- a quantitative study. J. Neurol. Sci., 56, 343-356, 1982.
Wilcock, G.K. 1993 Chapter 17, Future Research: Direction and Strategies. In 'The Management of Alzheimer's Disease'. Edited by G.K. Wilcock, Wrightson Biomedical Publishing Ltd, 1993.
Wild, H.M., Butler, S.R., Carden, D. and Kulikowski, J.J. 1985 Primate cortical area V4 important for colour constancy but not wavelength discrimination. Nature 313,, 133-135, 1985.
Winkler, I., and Naatanen, R. 1993 Event-related brain potentials to infrequent partial omissions in series of auditory stimuli. In H.-J. Heinze, G. R. Mangun and T.F. Münte (Eds.) New developments in evebt-related potentials, pp.219-226. Berlin: Birkhäuser, 1993.
Winkler,I., Reinikainen, K. and Naatanen, R. 1993 Event-related brain potentials reflect traces of echoic memory in humans. Perception and Psychophysics, 53, 443-449, 1993.
Winter, O., Kok, A., Kenemans, J.L. and Elton, M. 1995 Auditory event-related potentials to deviant stimuli during drowsiness and stage 2 sleep. Electroencephalography and Clinical Neurophysiology, 96, 398-412, 1995.
Woldorff, M.G., Fox, P.T., Matzke,M., Lancaster, J.L., Veeraswamy, S., Zamarripa, F., Seabolt, M., Glass, T., Gao, J.H., Martin, C.C. and Jerabek, P. 1997 Retinotopic organization of early visual spatial attention effects as revealed by PET and ERPs. Human Brain Mapping, 5, 280-286, 1997.
Woldorff, M.G., Hackley, S.A. and Hillyard, S.A. 1991 The effects of channel-selective attention on the mismatch negativity wave elicited by deviant tones. Psychophysiology, 28, 1, 30-42, 1991.
Woldorff, M.G. and Hillyard, S.A. 1990 Attentional influence on the mismatch negativity, p. 258-260, in Naatanen, 1990.

Woldorff, M. and Hillyard, S.A. 1991 Modulation of early auditory processing during selective listening to rapidly presented tones. Electroencephalography and Clinical Neurophysiology, 79, 170-191, 1991.
Wolfe, J.M., Cave, K.R. and Franzel, S.L. 1989 Guided search: an alternative to the feature integration model for visual search. J. Exp. Psychology, 15, 419-433, 1989.
Wolfe, J.M. 1992 Effortless texture segmentation and parallel visual search are not the same thing. Vision Research, 32, 757-763, 1992.
Wolfe, J.M. 1994 Guided Search 2.0. A revised model of visual search. Psychonomic Bulletin and Review, 1994, 1, (2), 202-238.
Wolfe, J.M., Cave, K.R. and Franzel, S.L. 1989 Guided search: an alternative to the feature integration model for visual search. J. of Experimental Psychology: Human Perception and Performance, Vol. 15, No. 3, 419-433, 1989.
Wolfe, N., Reed, B.R., Eberling, J.L. and Jagust, W.J. 1995 Temporal lobe perfusion on SPECT, predicts the rate of cognitive decline in Alzheimer's disease. Archives of Neurology, 52, 257-262, 1995.
Wong-Riley, M.T.T. 1979 Changes in the visual system of monocularly sutured or enucleated cats demonstrable with cytochrome oxidase histochemistry. Brain Research, 171, 11-28, 1979.
Woods, D.L. 1992 Auditory selective attention in middle-aged and elderly subjects: an event-related brain potential study. Electroencephalography and Clinical Neurophysiology, 84, 456-468, 1992.
Woods, D.L., Alho, K. and Algazi, A. 1992 Intermodal selective attention. I. Effects on event-related potentials to lateralized auditory and visual stimuli. Electroencephalography and clinical Neurophysiology, 82, 1992, 341-355.
World Health Organisation ICD-10 1992 cited in Lezak, 1995.
Wright, C.E. and Furlong, P.L. 1988 VEPs in elderly patients with primary or multi-infarct dementia. British J. of Psychiatry, 152, 679-682, 1988.
Wright,C.E., Harding, G.F.A. and Orwin, A. 1984 Presenile dementia-the use of the flash and pattern VEP in diagnosis. Electroencephalography and clinical Neurophysiology, 57, 405-415, 1984.
Wright, C.E., Drasdo, N. Harding, G.F.A. 1987 Pathology of the optic nerve and visual association areas. Brain, 110, 107-120, 1987.
Wright, C.E., Williams, D.E., Drasdo, N. and Harding, G.F.A. 1985 The influence of age on the eletroretinogram and VEP. Documenta Ophthalmological, 59, 365-384, 1985.
Wright, C.E., Harding, G.F. A. and Orwin, A. 1986 The flash and pattern VEP as a diagnostic indicator of dementia. Documenta Opthalmologica, 62, 89-96, 1986.
Wurtz,R.H., Goldberg, M.E. and Robinson, D.L. 1980 Behavioral modulations of visual responses in the monkey. In J.M. Sprague and A.N. Epstein, eds., Psychobiology and Physiological psyhology, 9, 43-83, New York: Academic Press, 1980.

Yum, L., Wolf, K.M. and Chiappinelli, V.A. 1996 Nicoyinic acetylcholine receptors in separate brain regions exhibit different affinities for methyllycaconitine. Neuroscience, 72 (2), 545-555, May, 1996.
Young, M.P. 1992 objective analysis of the topological organization of the primate cortical visual system. Nature, 358, 152-155, 1992.
Young, R.S.L. and Alpern, M. 1980 Pupil responses to foveal exchange of monochromatic lights. J. of the Optical society of America, 70, 697-706, 1980.

Zani, A. and Proverbio, A.M. 1997 Attention modulation of short latency ERPs be selective attention to conjunction of spatial frequency and location. J. of Psychophysiology, 11, 21-32, 1997.
Zeki, S. M. 1973 Color coding in rhesus monkey prestriate cortex. Brain research, 53, 422-427, 1973.
Zeki, S. 1978 (a) Uniformity and diversity of structure and function in rhesus monkey prestriate visual cortex. J. Physiology, 277, 273-290, 1978.
Zeki, S.M. 1978 (b) Functional specialization in the visual cortex of the rhesus monkey. Nature, 274, 423-428, 1978.
Zeki, S. 1983 The distribution of wavelength and orientation selective cells in different areas of monkey visual cortex. Proceedings of the Royal Society of London, B, 217, 449-470, 1983.
Zeki, S. 1990 A centuary of cerebral achromatopsia. Brain, 113, 1721-1777, 1990.
Zeki, S. 1993 A vision of the brain. Blackwell. Oxford, 1993.
Zeki, S., Watson, J.D.G., Lueck, C.J., Fristin. K.J., Kennard, C., Frackowiak, R.S.J. 1991 A direct demonstration of functional specialization in human visual cortex. The J. of Neuroscience, 11 (3), March, 1991.

Zeki, S. and Shipp, S. 1988 cited in Shiller and Logothetis, 1990.
Zelinsky, E.J. and Sheinberg, D.L. 1997 Eye movements during parallel-serial visual search. J. of Experimental psychology: Human perception and performance, 23, (1), 244-262, 1997.
Zerfass, R., Sattel, H., Daniel, S., Besthorn, C. and Förstl, H. 1995 Pupillary response to Tropicamide: not a simple bedside test for Alzheimer's disease. International J. of Geriatric psychiatry, Vol. 10, 995-997, 1995.
Zihl, J. 1980 Blindsight: improvement of visually guided eye movements by systematic practice in patients with cerebral blindness. Neuropsychologia, 18, 71-77, 1980.
Zipser, Lee, Lamme and Achiller 1994. Cited in Schiller, 1996.

APPENDICES

CHAPTER THREE APPENDIX

TABLE A3.1 (STUDY ONE).

The mean difference in negativity between the deviant and standard stimuli (deviant -standard amplitude [μV]).

Electrode site	150-280 msec epoch	280-400 msec epoch
T5	1.26	1.68
O1	1.25	1.78

TABLE A3.2 (STUDY TWO).

The mean difference in negativity between the deviant and standard stimuli (deviant -standard amplitude [μV]).

Electrode site	150-280 msec epoch	280-400 msec epoch
T6	0.5	-0.2
O2	0.81	0.29

TABLE A 3.3 (STUDY THREE).

The mean difference in negativity between the deviant and standard stimuli (deviant -standard amplitude [μV]).

Electrode site	150-280 msec epoch	280-400
T5	2.86	3.84
T6	2.64	2.85
O1	3.15	3.76
O2	3.41	3.95
Oz	2.65	3.15

TABLE A 3.4 (24 subjects)

The mean difference in negativity between the deviant and standard stimuli (deviant -standard amplitude [μV]).

Electrode site	150-280	280-400
T5	2.9	2.99
T6	3.11	2.92
O1	3.18	3.13

O2	3.32	3.4
Oz	2.69	2.7

TABLE A 3.5 (swapping standards and deviants)

The mean difference in negativity between the deviant and standard stimuli (deviant -standard amplitude [μV]).

Electrode site	150-280	280-400
T5	0.7	2.11
T6	0.55	1.93
O1	0.84	2.4
O2	0.68	2.49
Oz	0.36	1.8

TABLE A 3.6 (study five; 12 older adults)

The mean difference in negativity between the deviant and standard stimuli (deviant -standard amplitude [μV]).

Electrode site	150-280 msec	280-400 msec
T5	0.99	0.11
T6	1.38	0.38
O1	1.54	0.31
O2	1.93	0.92
Oz	1.45	0.56

TABLE A 3.7 (study six: 8 young adults)

The mean difference in negativity between the deviant and standard stimuli (deviant -standard amplitude [μV]).

Electrode site	150-280 msec	280-400 msec
T5	2.6	3.42
T6	2.07	1.97
O1	2.52	3.01
O2	2.88	3.03
Oz	2.18	2.52

TABLE A3.8 (study six: 8 older adults)

The mean difference in negativity between the deviant and standard stimuli (deviant -standard amplitude [μV]).

Electrode site	150-280 msec	280-400 msec
T5	1.21	0.12
T6	1.59	0.68
O1	1.84	0.34
O2	2.22	0.93
Oz	1.87	0.64

TABLE A 3.9 (study six; 8 AD adults)

The mean difference in negativity between the deviant and standard stimuli (deviant -standard amplitude [μV]).

Electrode site	150-280 msec	280-400 msec
T5	2.14	1.48
T6	1.93	0.73
O1	2.22	1.68
O2	2.42	1.18
Oz	1.79	1.23

TABLE A 3.10

The mean difference in VMMN amplitude (μV) between 12 old and 12 young participants

Electrode site	150-280 msec	280-400 msec
T5	1.87	3.73
T6	1.26	2.47
O1	1.61	3.45
O2	1.48	3.03
Oz	1.19	2.58

TABLE A 3.11

The mean difference in VMMN amplitude (μV) between 8 old and 8 young participants

Electrode site	150-280 msec	280-400 msec
T5	1.4	3.29
T6	0.48	1.29
O1	0.67	2.67
O2	0.66	2.09
Oz	0.3	1.88

TABLE A 3.12

The mean difference in VMMN amplitude (μV) between 8 old and 8 old adults with AD

Electrode site	150-280 msec	280-400 msec
T5	0.94	1.36
T6	0.34	0.04
O1	0.38	1.34
O2	0.2	0.24
Oz	-0.08	0.59

CHAPTER FOUR APPENDIX

TABLE A 4.1 INDICATING THE MEAN REACTION TIME PER INDIVIDUAL FOR 16, 36 AND 81 DISTRACTORS (ITEMS) FOR THE POP-OUT TASK FOR THE TARGET PRESENT CONDITION FOR YOUNG ADULTS.

		Number of distractors				
Subject	16	36	81	Slope (msec/item)	Intercept (msec)	r
1	494.07	437.4	492.53	0.19	466.4	0.19
2	499.2	465.2	454.27	-0.62	500.2	-0.87
3	474.6	420.6	446.93	-0.25	458.7	-0.31
4	627.27	539.8	605.2	-0.036	592.12	-0.03
5	464.6	477.4	494.47	0.45	459.05	0.99
MEAN	511.9	468.1	498.7	-0.053	495.3	-0.006
SD	65.9	41.1	56.7	0.37	50.8	0.6

TABLE A 4.2 INDICATING THE MEAN REACTION TIME PER INDIVIDUAL FOR 16, 36 AND 81 DISTRACTORS FOR THE POP-OUT TASK FOR THE TARGET PRESENT CONDITION FOR OLDER ADULTS.

		Number of Distractors				
Subject	16	36	81	Slope (msec/item)	Intercept (msec)	r
1	567.13	597.0	565.0	-0.15	582.9	-0.3
2	789.27	851.0	669.87	-2.21	867.9	-0.8
3	775.2	715.73	823.2	1.02	726.3	0.6
4	701.53	741.73	772.27	1.02	693.3	0.9
5	628.0	630.07	676.07	0.79	609.8	0.96
MEAN	692.2	707.1	701.3	0.094	696.0	0.3
SD	85	89.5	89.6	1.2	100.7	0.7

TABLE A 4.3 INDICATING THE MEAN REACTION TIME PER INDIVIDUAL FOR 16, 36 AND 81 DISTRACTORS FOR THE POP-OUT TASK FOR THE TARGET PRESENT CONDITION FOR OLDER ADULTS WITH ALZHEIMER'S DISEASE.

		Number of Distractors				
Subject	16	36	81	Slope (msec/item)	Intercept (msec)	r
1	1247.0	1102.73	1307.07	1.54	1150.8	0.5
2	988.93	777.93	1001.53	1.0	878.39	0.3
3	944.4	1044.27	1044.8	1.29	954.2	0.7
4	771.4	806.13	1310.13	8.78	573.3	0.97
5	44465.8	4032.9	5487.87	18.53	3840.5	0.83
MEAN	1683.5	1552.8	2030.3	6.2	1479.4	0.66
SD	13999.5	1246.6	1733.6	6.8	1195.1	0.24

TABLE A 4.4 INDICATING THE MEAN REACTION TIME PER INDIVIDUAL FOR 16, 36 AND 81 DISTRACTORS FOR THE POP-OUT TASK FOR THE TARGET ABSENT CONDITION FOR YOUNG ADULTS.

		Number of Distractors				
Subject	16	36	81	Slope (msec/item)	Intercept (msec)	r
1	640.93	681.2	774.93	2.065	607.5	0.99
2	571	628.27	639.87	0.923	572.09	0.8
3	673.2	704.93	759.53	1.308	654.53	0.99
4	728.6	748.4	980.0	4.084	637.94	0.97
5	717.4	728.07	734.47	0.24	715.9	0.93
MEAN	666.2	698.2	777.8	1.7	637.6	0.94
SD	57	41.6	111.5	1.3	48.2	0.07

TABLE A 4.5 INDICATING THE MEAN REACTION TIME PER INDIVIDUAL FOR 16, 36 AND 81 DISTRACTORS FOR THE POP-OUT TASK FOR THE TARGET ABSENT CONDITION FOR OLDER ADULTS.

		Number of Distractors				
Subject	16	36	81	Slope (msec/item)	Intercept (msec/item)	r
1	678.93	729.53	814.53	2.05	649.99	0.99
2	997.73	968.4	979.8	-0.18	990.24	-0.42
3	1933.6	2385.33	2027.33	-0.15	2121.9	-0.02
4	1143.2	1417.73	1307.07	1.68	1214.9	0.4
5	879.6	934.07	1007.07	1.9	855.85	0.99
MEAN	1126.6	1287.0	1227.2	1.06	1166.6	0.388
SD	431.2	593.3	430.5	1.0	511.8	0.6

TABLE A 4.6 INDICATING THE MEAN REACTION TIME PER INDIVIDUAL FOR 16, 36 AND 81 DISTRACTORS FOR THE POP-OUT TASK FOR THE TARGET ABSENT CONDITION FOR OLDER ADULTS WITH ALZHEIMER'S DISEASE.

		Number of Distractors				
Subject	16	36	81	Slope (msec/item)	Intercept (msec/item)	r
1	1993.07	2340.67	2429.53	5.91	1992.3	0.85
2	5502.0	6806.33	5677.07	-2	6084.1	-0.9
3	1299.27	1297.22	1574.27	4.56	1188.2	0.95
4	1895.07	1924.13	1973.67	1.19	1878.2	0.99
5	6728.4	6631.3	7007.9	4.99	6568.05	0.85
MEAN	3483.6	3799.9	3732.5	2.93	3542.2	0.5
SD	2196.3	24406.9	2189	2.9	2294.8	0.73

TABLE A 4.7 INDICATING THE MEAN REACTION TIME PER INDIVIDUAL FOR 16, 36 AND 81 DISTRACTORS FOR THE SERIAL TASK FOR THE TARGET PRESENT CONDITION FOR YOUNG ADULTS.

		Number of Distractors				
Subject	16	36	81	Slope (msec/item)	Intercept (msec/item)	r
1	536.67	611.07	611.33	0.96	544	0.7
2	820.53	833.73	987	2.7	760.54	0.97
3	546.33	625.93	847.07	4.68	465.83	0.99
4	582.33	783.6	833	3.39	582.7	0.8
5	829.6	775.01	809.4	-0.13	810.4	-0.2
MEAN	663.1	725.9	817.6	2.3	632.7	0.65
SD	133.2	90.1	120.3	1.7	131.3	0.44

TABLE A 4.8 INDICATING THE MEAN REACTION TIME PER INDIVIDUAL FOR 16, 36 AND 81 DISTRACTORS FOR THE SERIAL TASK FOR THE TARGET PRESENT CONDITION FOR OLDER ADULTS.

		Number of Distractors				
Subject	16	36	81	Slope (msec/item)	Intercept (msec)	r
1	744.67	835.07	951.73	3.085	707.04	0.99
2	933.93	1010.13	1043.13	1.52	928.35	0.9
3	1252.33	1194	1673.47	7.19	1054.71	0.9
4	890.53	1150.73	1001.4	0.86	976.282	0.22
5	850.53	1077.87	1498.27	9.86	705.104	0.99
MEAN	934.3	1053.6	1233.6	4.5	874.3	0.8
SD	171.1	126	294.3	3.9	143.2	0.29

TABLE A 4.9 INDICATING THE MEAN REACTION TIME PER INDIVIDUAL FOR 16, 36 AND 81 DISTRACTORS FOR THE SERIAL TASK FOR THE TARGET PRESENT CONDITION FOR OLDER ADULTS WITH ALZHEIMER'S DISEASE.

		Number of Distractors				
Subject	16	36	81	Slope (msec/item)	Intercept (msec)	r
1	1267.2	1329.4	2325.53	17.27	874.96	0.97
2	1418.87	1571.2	3273.93	30.11	753.01	0.97
3	2600.2	2014.4	2630.67	2.7	2295.112	0.3
4	1278.33	1691.73	2724.4	22.36	906.6	0.99
5	3346.53	5310.13	6448.73	43.94	3086.97	0.93
MEAN	1982.2	2383.4	3480.7	23.3	1583.3	0.83
SD	844.7	1479.9	1515.3	13.7	939.9	0.26

TABLE A 4.10 INDICATING THE MEAN REACTION TIME PER INDIVIDUAL FOR 16, 36 AND 81 DISTRACTORS FOR THE SERIAL TASK FOR THE TARGET ABSENT CONDITION FOR YOUNG ADULTS.

		Number of Distractors				
Subject	16	36	81	Slope (msec/item)	Intercept (msec)	r
1	762.53	1119.4	1469.87	10.36	658.03	0.97
2	993.53	1580.93	1999.87	14.44	884.7	0.95
3	846.2	1387.2	1576.8	10.05	824.5	0.88
4	860.33	1293.8	1820.53	14.25	692.9	0.99
5	902	1358.73	1568.2	9.3	863.9	0.91
MEAN	872.9	1348	1687.1	11.68	784.8	0.94
SD	75.4	149.1	194.5	2.2	92	0.04

TABLE A 4.11 INDICATING THE MEAN REACTION TIME PER INDIVIDUAL FOR 16, 36 AND 81 DISTRACTORS FOR THE SERIAL TASK FOR THE TARGET ABSENT CONDITION FOR OLDER ADULTS.

		Number of Distractors				
Subject	16	36	81	Slope (msec/item)	Intercept (msec)	r
1	821.53	1153.4	1474.2	9.55	726.4	0.97
2	1588.2	2135.53	2317.13	9.99	1570.3	0.87
3	2001.93	2661.8	3852.6	28.13	1591.6	0.99
4	1478.67	1706.4	1951.8	6.97	1403.3	0.98
5	1610.8	1885.2	2585.27	15.09	1358.2	0.99
MEAN	1500.2	1908.5	2436.2	13.9	1329.9	0.96
SD	382.8	496.1	800.3	7.6	315.2	0.045

TABLE A 4.12 INDICATING THE MEAN REACTION TIME PER INDIVIDUAL FOR 16, 36 AND 81 DISTRACTORS FOR THE SERIAL TASK FOR THE TARGET ABSENT CONDITION FOR OLDER ADULTS WITH ALZHEIMER'S DISEASE.

		Number of Distractors				
Subject	16	36	81	Slope (msec/item)	Intercept (msec)	r
1	1850	2405.07	2752.33	12.84	1766.6	0.94
2	4593.93	6121.67	7007.67	34.18	4392.3	0.93
3	2430	2509.4	3201.8	12.47	2160.9	0.98
4	1929.13	2994.87	3518.33	22.28	1826.3	0.92
5	7941.93	7434.67	7224.47	-9.96	7975.3	-0.9
MEAN	3748.9	4293.1	4740.9	14.4	3624.3	0.6
SD	2321.7	2080.6	1955.7	14.5	2381	0.73

TABLE A4:13 INDICATING THE MEAN % CORRECT RESPONSES

(A) POP-OUT VISUAL SEARCH TASK: TARGET PRESENT : YOUNG ADULTS

		YOUNG ADULTS		
PARTICIPANT	NUMBER OF DISTRACTORS			% COLLAPSED ACROSS DISTRACTORS
	16	36	81	
1	100	100	100	100
2	100	100	100	100
3	100	100	100	100
4	100	100	100	100
5	86.67	100	100	95.6
MEAN	97.33	100	100	99.11
sd	5.9	0	0	1.76

(B) POP-OUT VISUAL SEARCH TASK: TARGET PRESENT: OLDER ADULTS

		OLDER ADULTS		
PARTICIPANT	NUMBER OF DISTRACTORS			% COLLAPSED ACROSS DISTRACTORS
	16	36	81	
1	100	93.33	93.33	95.6
2	100	93.33	86.67	93.3
3	100	100	100	100
4	93.33	100	93.33	95.6
5	100	93.33	100	97.8
MEAN	98.66	96	94.66	96.4
sd	2.9	3.7	5.6	2.27

(C) POP-OUT VISUAL SEARCH TASK: TARGET PRESENT: OLDER ADULTS WITH ALZHEIMER'S DISEASE

		Alzheimer's ADULTS		
PARTICIPANT	NUMBER OF DISTRACTORS			% COLLAPSED ACROSS DISTRACTORS
	16	36	81	
1	100	100	93.33	97.8
2	100	100	100	100
3	86.67	93.33	86.67	88.9
4	100	100	100	100
5	60	80	86.67	75.6
MEAN	89.3	94.7	93.3	92.4
sd	17.4	8.7	6.0	9.4

(D) SERIAL VISUAL SEARCH TASK: TARGET PRESENT : YOUNG ADULTS

		YOUNG ADULTS		
PARTICIPANT	NUMBER OF DISTRACTORS			% COLLAPSED ACROSS DISTRACTORS
	16	36	81	
1	100	100	100	100
2	93.33	100	93.33	95.6
3	100	100	93.33	97.8
4	100	93.33	100	97.8
5	100	86.67	93.33	93.3
MEAN	98.7	96	96	96.9
sd	2.7	5.3	3.3	2.3

(E) SERIAL VISUAL SEARCH TASK: TARGET PRESENT : OLDER ADULTS

		OLDER ADULTS		
PARTICIPANT	NUMBER OF DISTRACTORS			% COLLAPSED ACROSS DISTRACTORS
	16	36	81	
1	100	100	100	100
2	100	93.33	93.33	95.6
3	93.3	100	93.33	95.6
4	93.3	93.33	100	95.6
5	100	93.33	73.33	88.9
MEAN	97.3	96	92	95.1
sd	3.3	3.3	9.8	3.6

(F) SERIAL VISUAL SEARCH TASK: TARGET PRESENT : OLDER ADULTS WITH ALZHEIMER'S DISEASE.

		Alzheimer's ADULTS		
PARTICIPANT	NUMBER OF DISTRACTORS			% COLLAPSED ACROSS DISTRACTORS
	16	36	81	
1	100	80	46.67	75.6
2	93.33	93.33	100	95.6
3	93.33	86.67	53.33	77.8
4	93.33	80	46.67	73.3
5	93.33	73.33	80	82.2
MEAN	94.7	82.7	65.3	80.9
sd	2.7	6.8	21.2	7.9

POP-OUT VISUAL SEARCH TASK: TARGET ABSENT : YOUNG ADULTS

		YOUNG ADULTS		
PARTICIPANT	NUMBER OF DISTRACTORS			% COLLAPSED ACROSS DISTRACTORS

	16	36	81	
1	100	100	100	100
2	100	100	100	100
3	100	100	100	100
4	100	100	93.33	97.8
5	100	100	100	100
MEAN	100	100	98.7	99.6
sd	0	0	2.7	0.88

(H) POP-OUT VISUAL SEARCH TASK: TARGET ABSENT : OLDER ADULTS

		OLDER ADULTS		
PARTICIPANT	NUMBER OF DISTRACTORS			% COLLAPSED ACROSS DISTRACTORS
	16	36	81	
1	100	100	100	100
2	100	100	100	100
3	100	100	100	100
4	100	93.33	100	97.8
5	100	100	100	100
MEAN	100	98.66	100	99.5
sd	0	2.9	0	0.88

(I) POP-OUT VISUAL SEARCH TASK: TARGET ABSENT : OLDER ADULTS WITH ALZHEIMER'S DISEASE.

		Alzheimer's ADULTS		
PARTICIPANT	NUMBER OF DISTRACTORS			% COLLAPSED ACROSS DISTRACTORS
	16	36	81	
1	100	100	100	100
2	100	100	100	100
3	100	86.67	100	95.6
4	100	100	100	100
5	60	93.33	73.33	75.6
MEAN	92	96	94.7	94.24
sd	17.9	5.96	11.9	9.47

(J) SERIAL VISUAL SEARCH TASK: TARGET ABSENT : YOUNG ADULTS

		YOUNG ADULTS		
PARTICIPANT	NUMBER OF DISTRACTORS			% COLLAPSED ACROSS DISTRACTORS
	16	36	81	
1	100	100	100	100
2	100	100	100	100

3	100	100	100	100
4	100	100	100	100
5	100	100	100	100
MEAN	100	100	100	100
sd	0	0	0	0

(K) SERIAL VISUAL SEARCH TASK: TARGET ABSENT : OLDER ADULTS

		OLDER ADULTS		
PARTICIPANT	NUMBER OF DISTRACTORS			% COLLAPSED ACROSS DISTRACTORS
	16	36	81	
1	100	100	100	100
2	100	100	100	100
3	100	100	100	100
4	100	100	100	100
5	100	100	100	100
MEAN	100	100	100	100
sd	0	0	0	0

(L) SERIAL VISUAL SEARCH TASK: TARGET ABSENT : OLDER ADULTS WITH ALZHEIMER'S DISEASE.

		Alzheimer's ADULTS		
PARTICIPANT	NUMBER OF DISTRACTORS			% COLLAPSED ACROSS DISTRACTORS
	16	36	81	
1	73.33	66.67	60	66.7
2	80	93.33	100	91.1
3	93.33	100	100	97.8
4	86.67	100	93.33	93.3
5	80	60	66.67	68.9
MEAN	82.7	84	84	83.6
sd	6.8	17.2	17.2	13.1

TABLE A4.13 RAW DATA FOR VISUAL SEARCH STUDY 1(a) THE CONJUNCTION SERIAL SEARCH: YOUNG ADULT GROUP.

		TARGET PRESENT				TARGET ABSENT	
Subject	Number of distractors	Reaction Time (msec)	Standard Deviation	% Correct	Reaction Time (msec)	Standard Deviation	% Correct
1	16	831.5	263.4	100	1128.21	376.61	100
	36	871.79	390.66	93.33	1571.43	1748.25	100
	81	1135.53	449.1	73.33	1531.14	584.76	100
2	16	479.85	135.33	86.67	655.68	270.35	100
	36	454.21	96.22	93.33	666.67	197.96	100
	81	556.78	163.35	86.67	868.13	272.52	100
3	16	600.73	170.58	86.67	703.3	162.46	100
	36	868.13	446.95	100	1029.3	506.34	93.33
	81	739.93	264.22	100	1615.38	508.61	100
4	16	641.03	76.77	100	1230.77	293.55	100
	36	992.67	399.72	100	2018.32	544.11	100
	81	879.12	305.92	100	2864.47	596.45	100
5	16	641	198.83	100	1395	558.71	100
	36	663	140.03	100	2190.48	640.05	100
	81	695.97	138.79	100	3750.92	1083.18	100
6	16	710.62	427.86	100	1128.21	308.63	100
	36	1018.32	479.39	100	1835.16	598.95	100
	81	659.34	128.02	100	2952.38	1063.09	100
7	16	479.85	104.8	86.67	615.38	66.33	100
	36	586.08	116.86	93.33	805.86	294.91	100
	81	670.33	124.95	80	699.63	182.78	100
8	16	787.55	195.55	100	1073.26	383.98	100
	36	992.67	351.49	100	1945.05	398.28	100
	81	908.42	589.17	93.33	2714.29	531.82	100
9	16	948.72	285.1	100	1091.58	218.67	100
	36	989.01	166.14	100	1750.92	923.59	100
	81	1051.28	245.6	100	1996.34	847.57	100
10	16	626.37	195.7	100	1106.23	373.73	100
	36	934.07	566.07	93.33	1710.62	507.79	100
	81	747.25	318.22	100	1978.02	407.48	100
11	16	644.69	160.15	100	728.94	84.27	100
	36	681.32	204.32	100	1032.97	248.51	100
	81	714.29	160.86	100	1087.91	373.95	100

12	16	684.98	242.07	93.33	901.1	185.52	100

	36	750.2	382.18	93.33	1333.33	351.49	100
	81	853.48	450.64	93.33	2091.58	523.51	100
13	16	989.01	987.92	86.67	1058.61	212.26	93.33
	36	1128.21	397.77	86.67	1380.95	512.86	100
	81	860.81	172.09	100	1699.63	816.15	100
14	16	915.75	321.5	93.33	1567.77	1013.96	93.33
	36	1388.28	823.51	93.33	1963.37	493.84	100
	81	1003.66	332.58	93.33	2040.29	859.24	100
15	16	582.42	107.51	100	750.92	172.09	100
	36	703.3	203.69	86.67	1018.32	212.67	100
	81	706.96	211.65	93.33	1315.02	328.01	100
16	16	589.74	127.12	100	1054.95	225.78	100
	36	875.46	426.35	100	1835.16	704.5	100
	81	853.48	403.69	100	3424.91	1359.05	100
17	16	695.97	241	100	1179.49	204.39	93.33
	36	743.59	184.43	100	2337	355.4	100
	81	864.47	266.33	100	4545.79	1024.87	100
18	16	681.32	161.93	93.33	890.11	345.76	100
	36	699.63	257.27	100	1190.48	374.77	93.33
	81	941.39	525.73	93.33	1234.43	322.31	100
19	16	637.36	179.61	86.67	772.89	181.6	100
	36	736.26	269.01	93.33	952.38	173.34	100
	81	831.5	260.93	80	1157.51	128.8	100
20	16	655.68	104.8	100	1014.65	202.27	100
	36	754.58	236.3	100	1146.52	264.22	93.33
	81	941.39	500.52	100	1219.78	170.24	100
21	16	845.07	195.56	100	1156.93	402.55	100
	36	826.33	149.95	100	1247.27	220.33	100
	81	900.93	197.87	93.33	1500.33	320.31	100
22	16	600.73	114.63	100	813.19	334.35	100
	36	717.95	255.59	93.33	743.59	122.63	100
	81	652.01	142.17	80	813.19	136.5	100
23	16	725.27	232.37	93.33	1054.94	180.09	100
	36	805.86	230.94	93.33	1787.55	284.64	100
	81	769.23	324.4	100	2146.52	742.55	100

24	16	714.29	176.22	93.33	915.75	132.43	93.33
	36	769.23	217.81	100	1058.61	232.62	100
	81	992.67	371.19	86.67	1366.3	373.16	100

25	16	641.03	188.82	100	1238.1	265.84	100
	36	882.78	489.45	100	2168.5	678.32	100
	81	875.46	647.62	100	2857.14	650.12	100

TABLE A4.14 RAW DATA FOR VISUAL SEARCH STUDY 1(a) THE CONJUNCTION SERIAL SEARCH: OLDER ADULT GROUP.

			Target Present			Target Absent	
Subject	Number of Distractors	Reaction Time (msec)	Standard deviation	% Correct	Reaction Time (msec)	Standard deviation	% Correct
1	16	1201.47	611.8	93.33	1912.09	446.95	100
	36	1498.17	962.15	93.33	2318.68	679.7	93.33
	81	1758.24	1016.54	93.33	2901.1	744.21	100
2	16	1054.95	252.81	100	1476.19	260.93	100
	36	1212.45	315.27	93.33	2172.16	415.8	100
	81	1663	554.71	93.33	2985.35	507.7	100
3	16	805.86	127.45	100	937.73	143.08	100
	36	1025.64	404.12	100	1091.58	230.2	100
	81	1014.65	386.78	86.67	1439.56	293.11	100
4	16	868.13	250.24	93.33	1058.61	296.96	100
	36	791.21	287.61	100	1150.18	327.35	100
	81	1010.99	421.94	100	1750.92	371.42	100
5	16	673.99	110.8	100	1095.24	267.14	100
	36	769.23	308.73	100	1457.88	243.84	100
	81	952.38	480.2	86.67	1593.41	361.49	100
6	16	582.42	202.2	100	1043.96	260.21	100
	36	681.32	227.3	100	1747.25	293.11	100
	81	684.98	250.82	100	2758.24	278	100
7	16	666.47			1393.33		
	36	961.13			1717.6		
	81	936			2072.67		

8	16	681.53	208.08	93.33	781	119.35	100
	36	781.13	200.25	86.67	915.53	194.31	100
	81	834.73	350.35	80	1042.93	157.69	100

9	16	1296.73	791.33	100	1446.6	664.21	100
	36	1284.33	649.57	93.33	1526.07	381.42	100
	81	1455.27	386.4	93.33	2631.07	2094.19	100

10	16	1069.07	217.54	93.33	1690.67	421.79	93.33
	36	1646.93	915.54	100	2792.4	1050.3	100
	81	2061.2	994.59	73.33	2543.07	335.08	93.33
11	16	1825.33	684.29	93.33	1991.87	409.85	100
	36	2420.33	829.22	66.67	2580.13	481.88	100
	81	2702.2	607.24	66.67	3287.07	457.8	100
12	16	833.33			1642.87		
	36	882.53			1873.87		
	81	881.33			2722.33		
13	16	839.8			3441.8		
	36	1049			2575.8		
	81	1288			3478.6		
14	16	864.47	208.16	100	1000	187.14	100
	36	1179.49	409.52	100	1501.83	404.12	100
	81	1128.2	372	80	2036.63	675.32	100
15	16	1326.01	390.66	93.33	1472.53	319.4	100
	36	1384.62	538.83	100	2190.48	391.21	93.33
	81	1344.32	659.62	100	3384.62	349.24	100
16	16	1010.99	451.56	100	915.75	198.83	93.33
	36	860.81	240.1	100	1296.7	214.62	100
	81	948.72	361.77	100	1787.55	265.03	100
17	16	1452.27			2562.4		
	36	1736.13			4250.47		
	81	1729.93			5142.93		
18	16	1027.67	514.95	100	1386.07	348.65	100
	36	1127.13	380.29	100	1936.47	450.06	100
	81	1066.33	233.27	100	2571.47	515.3	100
19	16	1132.53			4030.27		
	36	1662.2			5167.2		
	81	2113.33			6317.47		

20	16	1923.07			5139.13		
	36	1689.2			7476.93		
	81	3922.07			7741.07		
21	16	1161.17	349.28	100	1992.67	538.54	100
	36	1260.07	687.67	100	3479.85	1097.86	100
	81	1912.09	1001.41	93.33	6157.51	1048.59	100
22	16	1018.32	722.95	86.67	1512.82	337.34	100
	36	1278.39	639.24	86.67	2424.91	332.84	100
	81	1608.06	835.73	93.33	3109.89	517.02	100

23	16	1095.24	528.02	100	1553.11	550.81	100
	36	1472.53	649.52	100	3245.42	585.72	100
	81	1805.86	928.01	93.33	4912.09	862.98	100
24	16	1847.07	1130.88	93.33	2592.87	334.76	100
	36	1429.67	817.64	100	3344.47	392.97	100
	81	2627.73	1375.5	73.33	4964.2	718.66	100
25	16	1440.13	540.78	86.67	2062	574.95	93.33
	36	1474.13	611.79	86.67	2167	702.95	100
	81	2321.13	487.44	53.33	2624.33	395.76	100

ADULT GROUP. TABLE A4.15 RAW DATA FOR VISUAL SEARCH STUDY 1(b) THE SIZE SERIAL SEARCH: YOUNGER ADULTS.

			Target Present			Target Absent	
Subject	Number of Distractors	Reaction Time (msec)	Standard deviation	% Correct	Reaction Time (msec)	Standard deviation	% Correct
1	16	1069.6	367.92	100	1428.57	390.18	100
	36	1252.75	728.69	100	1714.29	463.53	100
	81	1728.94	970.27	86.67	2406.59	555.38	100
2	16	985.35	459.45	93.33	1721.61	652.33	93.33
	36	1062.27	516.54	93.33	1948.72	546.25	100
	81	1457.88	926.39	73.33	2534.8	659.62	100
3	16	882.78	325.37	86.67	1212.45	604.92	80
	36	886.45	354.79	80	1655.68	556.81	80
	81	1377.29	601.34	46.67	1992.67	580.17	100

4	16	1421.25	755.33	100	2970.7	582.4	100
	36	1333.33	633.14	100	4380	1235.52	100
	81	3417.58	2082.87	93.33	5816.85	1613.29	100
5	16	1208.79	620.24	100	2271.1	478.85	100
	36	1553.11	773.28	93.33	2827.84	546.64	100
	81	2142.86	953.71	80	3706.96	860.24	100
6	16	1626.37	1612.62	86.67	2201.47	645.28	100
	36	1326.01	591.36	86.67	2791.21	1005.27	100
	81	1743.59	948.83	66.67	2915.75	764.3	100
7	16	1043.96	452.14	66.67	1600.73	759.6	53.33
	36	1289.38	333.49	46.67	1655.68	669.68	86.67
	81	1597.1	590.12	53.33	1542.1	384.88	86.67

8	16	1161.17	476.68	100	1912.09	364.58	100
	36	1212.45	443.69	93.33	2194.14	277.43	100
	81	1853.48	531.69	60	2545.79	407.31	100
9	16	1494.51	440.15	100	4205.13	1412	86.67
	36	1725.27	724.72	100	4315.02	1339.59	100
	81	2377.29	1194.34	100	6468.86	1327.4	100
10	16	1032.97	567.29	100	2637.36	584.81	100
	36	1109.89	635.09	100	3205.13	707.21	100
	81	1582.42	649.85	100	4000	1065.67	100
11	16	824.18	278.62	100	2124.54	582.1	100
	36	948.72	514.37	93.33	2802.2	829.39	100
	81	1468.86	670.84	86.67	2175.82	657.64	100
12	16	772.89	370.02	86.67	1377.29	407.73	100
	36	761.9	374.31	100	1380.95	591	100
	81	1146.52	602.92	60	1479.85	500.77	100
13	16	1029.3	355.15	100	1509.16	506.09	93.33
	36	1326.01	588.07	93.33	2267.4	565.87	100
	81	1857.14	946.72	86.67	2853.48	609.89	100
14	16	1388.28	483.69	86.67	2307.69	989.66	93.33
	36	1747.25	675.56	66.67	2556.78	814.93	100
	81	1963.37	507.62	53.33	2505.49	582.15	93.33
15	16	897.44	461.42	93.33	1424.91	482.8	93.33
	36	1065.93	405.25	93.33	1684.98	511.51	100
	81	1278.39	667.29	73.33	2153	1020.81	100
16	16	1080.59	483.78	100	2989.01	972.25	100
	36	1234.43	833.77	100	4633.7	1017.52	100
	81	2194.14	1410.57	93.33	6945.05	1624.61	100

17	16	1571.43	685.26	93.33	2384.62	537.07	100
	36	1985.35	1318.82	93.33	3362.64	888.2	100
	81	2509.16	15564.13	80	4970.7	1502.71	93.33
18	16	761.9	390.66	93.33	1194.14	317.32	100
	36	783.88	334.52	86.67	1296.7	403.12	86.67
	81	948.72	477.41	80	1252.75	297.49	100
19	16	1084.25	308.35	93.33	1630.04	360.1	100
	36	1201.47	499.22	80	1820.51	236.66	93.33
	81	1644.69	595.22	46.67	2091.57	336.45	80
20	16	989.01	306.63	100	2003.66	340.52	100
	36	1051.28	343.68	100	2758.24	479.09	100
	81	1637.36	711.93	93.33	3351.65	816.82	100
21	16	1482.13	802.4	100	3668.87	1699.94	100
	36	1804.87	1130.73	93.33	3971.67	1124.43	100
	81	2458.2	1489.66	93.33	4000.4	1671.07	100

22	16	945.05	260.38	93.33	1190.48	262.41	100
	36	1014.65	240.28	86.67	1274.73	177.68	100
	81	1212.45	278.21	53.33	1388.28	289.6	100
23	16	1256.41	456.82	100	3065.93	750.56	100
	36	1362.64	374.5	100	3728.94	521.2	100
	81	2311.36	1278.07	66.67	4260.07	578.09	100
24	16	1054.95	397.41	86.67	1534.8	346.55	100
	36	1545.79	748.45	80	2135.53	588.44	93.33
	81	2454.21	386.66	26.67	2597.07	692.98	100
25	16	1318.68	760.49	93.33	2542.12	652.59	100
	36	1813.19	1098.31	86.67	3974.36	1461.35	100
	81	2728.94	1962	80	4835.17	1419.79	100

ADULT GROUP. TABLE A4.16 RAW DATA FOR VISUAL SEARCH STUDY 1(b) THE SIZE SERIAL SEARCH: OLDER ADULTS.

			Target Present			Target Absent	
Subject	Number of Distractors	Reaction Time (msec)	Standard deviation	% Correct	Reaction Time (msec)	Standard deviation	% Correct.
1	16	3402.93	1686.31	86.67	5080.59	1432.62	100
	36	3871.8	2915.04	73.33	5065.93	1522.43	100
	81	4274.73	2329.66	53.33	6084.25	2240.51	100
2	16	1875.46	1004.56	93.33	3479.85	660.21	93.33
	36	1695.97	747.58	100	4139.19	921.67	93.33
	81	2926.74	1829.58	86.67	5058.61	599.55	100
3	16	1157.51	413.51	86.67	1567.77	480.29	100
	36	1234.43	436.05	93.33	1666.67	368.39	100
	81	1553.11	452.83	53.33	1776.56	259.11	100
4	16	992.67	630.4	100	2120.88	484.28	100
	36	1223.44	489.45	100	3040.29	704.15	100
	81	1974.36	1201.18	86.67	4604.4	1070.31	100
5	16	1205.13	465.05	80	1652.01	392.64	100
	36	1113.55	439.79	80	1681.32	331.5	100
	81	1604.4	545.59	53.33	2252.75	599.74	100
6	16	1157.51	394.29	93.33	2395.6	703.27	100
	36	1842.49	1071.45	100	3007.33	1352.82	93.33
	81	1637.36	1057.75	86.67	5362.64	2302.34	100

7	16	940			1926.4		
	36	1008.27			2283.33		
	81	1412.93			2803		
8	16	1300.4	492.72	93.33	1859.27	1085.19	93.33
	36	1075.47	257.17	93.33	1728	386.76	93.33
	81	1614.13	564.45	66.67	2370.53	727.02	100
9	16	1843.2	924.13	100	2369.67	572.51	100
	36	1765.2	613.09	86.67	2799.87	427.76	100
	81	3141.8	1224.13	66.67	4190.13	977.83	100
10	16	1941.73	1715.89	86.67	2575.2	862.7	93.33
	36	1838.13	834.45	73.33	3004.33	1692.75	93.33
	81	2031.6	791.35	66.67	2821.4	487.07	100

11	16	1244.73	390.01	100	3113.27	789.6	100
	36	2402.13	873.44	100	4203.2	937.08	100
	81	3048	1835.27	60	4169.6	909.34	100
12	16	723.1			1728.6		
	36	1026.13			2276.5		
	81	968.6			3101.2		
13	16	1733.4			4003.4		
	36	3025.2			3990		
	81	2117.2			6306.4		
14	16	1450.55	662.86	86.67	2578.75	1113.03	100
	36	1780.22	1541.65	93.33	2985.35	924.24	100
	81	1926.74	724.62	66.67	3069.6	1277.97	100
15	16	1373.63	564.17	100	3307	457.92	100
	36	1380.95	940.94	100	4882.78	1045.17	93.33
	81	2791.21	1942.07	86.67	6131.87	697.42	100
16	16	868.13	170.24	100	2761.9	756.93	100
	36	1285.71	616.34	100	3717.95	599.26	100
	81	2736.26	1754.46	73.33	4981.69	631.16	100
17	16	900.6			2211.2		
	36	1604.53			3800.53		
	81	2236.33			4911.33		
18	16	1178	528.31	100	3902.93	1347.45	93.33
	36	1346.2	585.28	100	3927.6	816.96	100
	81	2505.27	1377.38	80	5694	1444.16	100
19	16	2162			6275.33		
	36	2455.8			7986.2		
	81	2955.53			7965.2		

20	16	834.13			2067.47		
	36	1434.13			4334.13		
	81	2447.53			7595.93		
21	16	2095.24	984.61	100	5124.54	1501	100
	36	2036.63	1302.14	93.33	6069.6	921.01	100
	81	3476.19	1996.52	93.33	7256.41	1002.33	100
22	16	1293.04	845.32	86.67	3208.79	1607.53	93.33
	36	1142.86	533.2	100	3714.29	1770.07	93.33
	81	2487.18	1335.65	73.33	5073.26	1784.25	100
23	16	1772.89	901.76	100	3659.34	1662.78	100
	36	1472.53	891.11	93.33	5344.32	2276.5	100
	81	3703.3	1878.35	53.33	5692.31	1622.75	100
24	16	932	351.42	100	1998.87	812.5	93.33
	36	1262.07	689.1	100	3235.93	498.01	100
	81	1165.07	647.2	100	4907.13	819.96	100
25	16	2372.53	1052.15	100	4055.53	1272.27	100
	36	4198.6	2167.11	66.67	5244.4	2028.18	100
	81	4794.6	2048.55	53.33	6008.73	1242.46	93.33

TABLE 4.17 INDICATING THE MEAN SLOPE AND INTERCEPT VALUES FOR EXPERIMENT (2a) THE CONJUNCTION TASK, FOR YOUNG ADULTS.

Subject	AGE (years)	male or female	SLOPE (msec/ item) Target Present (TP)	SLOPE (msec/ item) Target Absent (TA)	SLOPE (msec/ item) Mean of TP&TA	Intercept (msec) Target Present (TP)	Intercept (msec) Target Absent (TA)	Intercept (msec) Mean of TP&TA
1	21	M	4.9	5	4.95	730	1188.6	959.4
2	22	M	1.4	3.5	2.4	436.3	576.2	506.2
3	23	F	1.3	13.9	7.6	678.8	501.5	590.1
4	28	M	2.6	24.1	13.3	721.6	971.1	846.3
5	23	F	0.8	36	18.4	630	850.9	740.5
6	27	M	-2	27.5	12.8	885	752	818.5
7	27	M	2.8	0.7	1.71	456.8	676.9	566.8
8	21	M	1.2	23.9	12.5	841.8	852.7	847.2
9	22	F	1.5	12.5	7	927.8	1059.3	993.7
10	31	M	0.8	12.1	6.5	731.9	1059.7	895.8
11	30	F	1	4.8	2.9	635.2	737.4	686.2
12	31	F	2.5	18.1	10.3	650.6	641	645.7
13	32	M	-2.6	9.4	3.4	1036.6	963.4	1036.6
14	39	M	-0.3	6.3	3	1116.9	1576.6	1346.7
15	39	M	1.6	8.3	5	593	659	626.1
16	38	M	3.3	36.3	19.8	627.1	497.1	562
17	32	M	2.6	51.3	27	652.4	411.7	532
18	31	F	4.2	4.6	4.4	586.4	902.6	744.5
19	41	F	2.8	5.7	4.3	609.2	708.8	658.9
20	47	M	4.4	2.9	3.6	590.8	998.5	794.7
21	48	F	1	5.3	3.2	813.4	1064.7	939
22	44	M	0.4	0.3	0.3	638.8	778.4	708.7
23	42	M	0.4	15.3	7.9	748	984.6	866.3
24	41	M	4.4	6.9	5.7	630.4	807	718.7
25	42	M	3	23.3	13.1	668.1	1055.7	861.9
Mean	32.6		1.76	14.32	8.04	705.5	851	779.7
Standard deviation	8.9		1.8	12.7	6.4	156.5	249.9	186.6

TABLE 4.18 INDICATING THE MEAN SLOPE AND INTERCEPT VALUES FOR EXPERIMENT (2a) THE CONJUNCTION TASK, FOR OLDER ADULTS.

Subject	Male or Female	Age (years)	SLOPE (msec/ item) Target Present (TP)	SLOPE (msec/ item) Target Absent (TA)	MEAN SLOPE (msec/ item) (TP) & (TA)	Intercept (msec) Target Present (TP)	Intercept (msec) Target Absent (TA)	Intercept (msec) MEAN of (TP)& (TA)
1	F	56	8.1	14.8	11.5	1127.1	1719.8	1423.4
2	M	50	9.5	22.3	15.9	890.5	1220.5	1055.5
3	F	54	2.6	7.7	5.2	832.2	813.9	823.1
4	M	52	2.7	11.1	6.9	772.5	827.5	800
5	F	50	4.2	6.9	5.6	610.3	1077.3	843.8
6	F	54	1.3	25.7	13.5	590.8	709.9	650.4
7	M	53	3.4	10	6.7	705.9	1283.7	994.9
8	M	52	2.2	3.8	3	670	743.5	706.8
9	F	55	2.7	19.3	10.9	1227.1	1012.5	1119.8
10	F	67	14.2	10	12.1	961.1	1900.6	1430.9
11	F	62	12.3	19.2	15.7	1772.1	1767.9	1770
12	F	68	0.6	17	8.8	838.7	1326.6	1082.7
13	M	62	6.6	3.9	5.2	765.1	2994.1	1879.6
14	F	62	3.2	15.3	9.2	916.5	836.3	876.4
15	M	62	0.1	28.9	14.5	1348	1066.7	1207.4
16	F	62	-0.5	13	6.3	960.8	757.5	859.2
17	F	67	3.5	36.3	19.9	1483.1	2374.2	1928.7
18	F	68	0.3	17.5	8.9	1061.9	1187.1	1124.5
19	F	76	14.2	33.6	23.9	1005	3683.9	2344.5
20	M	72	33.9	34.3	34.1	1006	5267.2	3136.9
21	M	78	12	63.3	37.7	910.3	1070.3	990.3
22	F	75	8.8	23	15.9	912.5	1330	1121.3
23	F	79	10.3	49.2	29.8	999.6	1055.7	1027.7
24	M	72	14.5	36.4	25.4	1326.1	2020.1	1673.1
25	M	78	14.4	8.91	11.7	1104.73	1889.6	1497.2
MEAN		63.4	7.4	21.3	14.3	991.9	1597.5	1294.7
Standard deviation		9.4	7.4	14.3	9.2	272.1	1035.4	563.4

TABLE 4.19 INDICATING THE MEAN SLOPE AND INTERCEPT VALUES FOR EXPERIMENT (2b) THE SIZE TASK, FOR YOUNG ADULTS.

Subject	Male or Female	Age (years)	SLOPE (msec/ item) Target Present (TP)	SLOPE (msec/ item) Target Absent (TA)	MEAN SLOPE (msec/ item) (TP) & (TA)	Intercept (msec) Target Present (TP)	Intercept (msec) Target Absent (TA)	Intercept (msec) MEAN of (TP)& (TA)
1	M	21	10.2	15.1	12.7	897.4	1180.2	1038.8
2	M	22	7.5	12.6	10.1	834.8	1509.9	1172.4
3	F	23	8.2	11.2	9.7	686.8	1122	904.4
4	M	28	33.3	41.8	37.6	578.8	2537.4	1558.1
5	F	23	14.2	21.7	17.9	1007.3	1975.1	1491.3
6	M	27	3.1	9.6	6.3	1429.3	2210.6	1819.9
7	M	20	8.2	-1.2	3.5	945.4	1651.6	1298.3
8	M	21	11.3	9.4	10.3	909.9	1799.6	1354.8
9	F	22	13.7	37	25.4	1256.8	3354.6	2305
10	M	31	8.8	20.4	14.6	851.7	2376.2	1614
11	F	30	10.2	-1.7	4.2	628.6	2442.9	1535.8
12	F	31	6.2	1.7	3.6	617.9	1338.1	978
13	M	32	12.6	19.4	16	846.5	1350.6	1098.5
14	M	39	8.2	2.3	5.2	1337.7	2353.1	1845.4
15	M	39	5.7	11.1	8.4	829.3	1263.4	1046.4
16	M	38	17.8	59.3	38.6	712.1	2228.9	1470.4
17	M	32	14	39.1	26.5	1403.3	1839.2	1621.2
18	F	31	3	0.6	1.8	698.2	1222	960.1
19	F	41	8.8	6.9	7.9	918.7	1540.7	1229.6
20	M	47	10.5	19.5	15	760.8	1841.8	1301.3
21	F	48	14.9	4.3	9.6	1253.1	3687.7	2470.4
22	M	44	4.2	3	3.6	872.9	1153:5	1013.2
23	M	42	17.1	17.3	17.2	887.5	2919.8	1903.7
24	M	41	21.3	15.3	18.3	740.7	1410.3	1075.5
25	M	42	21.5	32.5	27	1001.8	2341	1671.4
MEAN		32.6	11.8	16.3	14.0	916.3	1946	1431.1
Standard deviation		8.9	6.6	15.3	10.0	239.4	681.2	405.7

TABLE 4.20 INDICATING THE MEAN SLOPE AND INTERCEPT VALUES FOR EXPERIMENT (2b) THE SIZE TASK, FOR OLDER ADULTS.

Subject	Male or Female	Age (years)	SLOPE (msec/ item)Target Present (TP)	SLOPE (msec/ item) Target Absent (TA)	MEAN SLOPE (msec/ item) (TP) & (TA)	Intercept (msec) Target Present (TP)	Intercept (msec) Target Absent (TA)	Intercept (msec) MEAN of (TP)& (TA)
1	F	56	12.7	15.6	11.7	3288.6	4824.4	4171.8
2	M	50	18.1	23.6	20.9	1365.2	3178	2271.6
3	F	54	6.3	3.1	4.7	1037.7	1533.7	1285.7
4	M	52	15.4	37.6	26.5	715.4	1587.2	1151.3
5	F	50	6.9	9.8	8.4	999.6	1426.4	1213
6	F	54	5.4	46.8	26.1	1308.1	1514.6	1411.4
7	M	53	7.6	13.2	10.4	785	1754.2	1269.6
8	M	52	6	9	7.5	1062.4	1589.1	1325.8
9	F	55	21.8	28.5	25.1	1284.8	1856.6	1570.3
10	F	67	1.9	2.5	2.2	1853.9	2691.3	2272.7
11	F	62	25.5	13.4	19.4	1102.1	3235.7	2168.9
12	F	68	2.9	20.6	11.8	776.4	1453.5	1115
13	M	62	1.5	38.1	19.8	2225.8	3075.5	2650.6
14	F	62	6.6	6.6	6.6	1424.9	2585.7	2011.4
15	M	62	23.4	40.8	32.1	810.3	2965.6	1888
16	F	62	29.3	33.1	31.3	329.7	2352	1338.6
17	F	67	19.4	38.7	29.1	718.3	1925.8	1322
18	F	68	21.3	29.5	25.4	731.2	3198.8	1965.1
19	F	76	12	21.5	16.8	1991.5	6454.8	4223.1
20	M	72	24.4	82.8	53.6	488.8	997.5	743.1
21	M	78	23.1	31.7	27.4	1513.6	4744.3	3128.9
22	F	75	20.3	28.9	24.6	740.3	2715.8	1728
23	F	79	33.1	27.3	30.2	850.5	3688.6	2269.6
24	M	72	2.6	43.5	23	1003.8	1454.1	1228.9
25	M	78	33.2	27.8	30.5	2316.7	3868.7	3092.7
MEAN		63.4	15.2	26.9	21.0	1228.9	2666.9	1952.7
Standard deviation		9.4	10.0	16.9	11.2	657.6	1285.1	895.7

CHAPTER FIVE APPENDIX

TABLE A 5.1 RAW DATA FOR MEAN PUPILLARY AREA FOR AD, OLDER ADULTS AND YOUNGER ADULTS FOR EPOCHS, A, 1, 2, 3, 4, and B. FOR THE RIGHT EYE ONLY.

(This table is continued over several pages).

	RIGHT EYE	GROUP		
EPOCH	PARTICIPANT	AD	OLDER ADULT	YOUNG ADULT
A (1 to 4 secs)	1	6.84	8.13	15.96
	2	12.5	6.16	8.83
	3	9.23	13.71	10.18
	4	4.98	6.63	7.55
	5	7.76	15.94	12.02
	6	10.48	7.08	20.4
	7	8.26	10.19	13.46
	8	8.32	8.28	9.74
	9	11.99	5.68	15.6
	10	10.17	16.8	21.57
	11	4.72	8.04	9.3
	12	28.71	9.74	13.55
		mean =10.33	mean = 9.70	mean = 13.18
		sd = 6.01	sd = 3.6	sd= 4.3
1 (4 to 5 secs)	1	6.66	8.12	16.65
	2	13.64	6.25	8.62
	3	9.27	13.97	10.06
	4	4.94	6.43	8.43
	5	8.00	16.82	12.08
	6	11.05	7.59	22.10
	7	7.77	10.50	13.70
	8	7.91	8.45	9.74
	9	11.74	5.87	16.70
	10	10.32	18.28	21.44
	11	4.34	8.48	9.66
	12	29.18	9.62	13.62
		mean = 10.40	mean = 10.03	mean = 13.57
		sd = 6.23	sd = 3.97	sd = 4.55
2 (6 to 7 secs)	1	5.56	5.42	11.65
	2	7.61	3.86	7.33
	3	5.97	11.23	7.54
	4	3.91	5.03	5.24
	5	5.77	9.69	7.50
	6	7.57	4.49	17.28
	7	6.16	6.69	8.39
	8	5.92	6.31	5.99
	9	10.60	3.50	10.38
	10	8.66	11.90	10.97
	11	3.50	6.98	6.25
	12	29.76	6.82	9.12
		mean = 8.41	mean = 6.83	mean = 8.97
		sd = 6.7	sd = 2.7	sd = 3.3

3 (14 to 15 secs)	1	6.46	6.4	13.32
	2	10.34	4.87	8.74
	3	7.25	12.75	8.85
	4	4.37	5.69	7.41
	5	6.89	13.19	10.31
	6	9.85	5.47	21.24
	7	5.87	7.41	10.35
	8	6.65	7.19	8.03
	9	11.41	4.12	14.86
	10	9.45	14.84	17.61
	11	3.3	8.94	8.4
	12	28.23	8.04	10.45
		mean = 9.17 sd = 6.5	mean = 8.24 sd = 3.5	mean = 11.63 sd = 4.3
4 (16 to 17 secs)	1	6.57	7.34	16.31
	2	12.57	5.93	10.25
	3	8.87	14.17	9.41
	4	4.84	6.61	9.38
	5	6.73	14.61	11.62
	6	9.97	6.34	23.35
	7	7.22	9.28	12.23
	8	7.25	8.28	10.63
	9	14.05	6.03	15.93
	10	10.89	17.89	22.04
	11	3.39	10.23	9.89
	12	27.98	9.97	12.75
		mean = 10.03 sd = 6.17	mean = 9.72 sd = 3.73	mean = 13.65 sd = 4.6
B (21 to 24 secs)	1	6.76	7.86	17.25
	2	14.11	6.55	10.92
	3	9.61	14.69	9.42
	4	4.51	6.87	10.42
	5	7.03	15.8	10.75
	6	10.37	6.45	21.3
	7	6.77	9.48	14.31
	8	7.17	8.6	10.68
	9	13.53	6.28	15.75
	10	10.55	18.34	25.4
	11	3.1	10.51	8.1
	12	26.84	9.72	14.0
		mean = 10.03 sd = 5.98	mean = 10.1 sd = 5.04	mean = 14.03 sd = 4.97

TABLE A5.2 How the mean relative pupillary response amplitudes (i.e. the mean relative pupillary constriction) (in square mm) between epoch 1 and epoch 2, for the AD, older and younger adult groups were determined.

To determine the relative response amplitude for each participant, for each group, for each epoch, the following formula is used:

mean pupillary area of epoch 1- mean pupillary area of epoch 2 / mean pupillary area of epoch 1

(Where the mean pupillary area for each individual per each epoch is illustrated in table A5.1).

The following table illustrates the relative response amplitude (constriction) for each participant for each group between epoch 1 and epoch 2.

	RELATIVE PUPILLARY CONSTRICTION		
PARTICIPANT	AD	OLDER ADULT	YOUNG ADULT
1	0.16551651	0.3325123	0.30033003
2	0.4420821	0.33824	0.1496519
3	0.355987	0.1961345	0.250497
4	0.22088502	0.2177293	0.3784104
5	0.27875	0.4239001	0.379139
6	0.3149321	0.4084321	0.2180995
7	0.207720072	0.3628571	0.3875912
8	0.2515802	0.2532544	0.3850102
9	0.0971039	0.40377478	0.3784431
10	0.1608527	0.3490153	0.4883395
11	0.1935483	0.17668867	0.353002
12	- 0.0198766	0.2910602	0.3303964
	Mean = 0.2213195 sd = 0.12	Mean = 0.31664941 sd = 0.08	Mean = 0.33324 sd = 0.087

TABLE A 5.3

Table A5.3 illustrates how the mean relative pupillary response amplitude (in square mm) between epoch 2 and epoch 3, for the AD, older and younger adult groups were determined.

To determine the relative response amplitude for each participant, for each group, the following formula was used:

mean pupillary area of epoch 2 - mean pupillary area of epoch 3 / mean pupillary area of epoch 2

(Where the mean pupillary area for each individual per each epoch is illustrated in table A5.1).

The following table illustrates the relative response amplitude for each participant for each group between epoch 2 and epoch 3.

PARTICIPANT	RELATIVE RESPONSE AMPLITUDE		
	AD	OLDER ADULT	YOUNGER ADULT
1	- 0.1618705	- 0.1808118	- 0.1433476
2	- 0.3587385	- 0.261658	- 0.1923601
3	- 0.2144053	- 0.1353517	- 0.17374
4	- 0.117647	- 0.1312127	- 0.4141221
5	- 0.1941074	- 0.3611971	- 0.3746666
6	- 0.3011889	- 0.2182628	- 0.2291666
7	0.0470779	- 0.1076233	- 0.2336114
8	- 0.1233108	- 0.1394611	- 0.3405676
9	- 0.076415	- 0.1771428	- 0.4315992
10	- 0.091224	- 0.2470588	- 0.6052871
11	0.0571428	- 0.2808022	- 0.344
12	0.0514112	- 0.178856	- 0.1458333
	Mean = - 0.1236062 sd = 0.128	Mean = - 0.2016223 sd = 0.07	Mean = - 0.3023584 sd = 0.13

TABLE A5.4

Table A5.4 illustrates how the mean relative pupillary response amplitude between epoch 3 and epoch 4, for the AD, older adult and younger adult groups were determined.

To determine the relative response amplitude for each participant, for each group, the following formula was used.

Mean pupillary area of epoch 3 - mean pupillary area of epoch 4 / mean pupillary area of epoch 3

(Where the mean pupillary area for each individual per epoch is illustrated in table A5.1)

The following table illustrates the relative response amplitude for each participant for each group, between epoch 3 and epoch 4.

	RELATIVE RESPONSE AMPLITUDE		
PARTICIPANT	AD	OLDER ADULT	YOUNGER ADULT
1	- 0.0170278	- 0.146875	- 0.2244744
2	- 0.2156673	- 0.2176591	- 0.1727688
3	- 0.2234482	- 0.1113725	- 0.0632768
4	- 0.1075514	- 0.1616871	- 0.2658569
5	0.023222	- 0.1076573	- 0.1270611
6	- 0.0121827	- 0.1590493	- 0.0993408
7	- 0.2299829	- 0.2523616	- 0.1816425
8	- 0.0902255	- 0.1515994	- 0.3237858
9	- 0.2313759	- 0.4635922	- 0.0720053
10	- 0.1523809	- 0.2055256	- 0.2515616
11	- 0.0272727	- 0.1442953	- 0.1773809
12	0.0088558	- 0.2400497	- 0.2200956
	Mean = - 0.1062531 sd = 0.096	Mean = - 0.1968103 sd = 0.09	Mean = - 0.1816 sd = 0.077

TABLE A5.5

Table A5.5 illustrates how the mean relative pupillary response amplitude between epoch A and epoch B, for the AD, older adult and younger adult groups were determined.

To determine the relative response amplitude for each participant, for each group, the following formula was used.

(mean pupillary area of epoch A - mean pupillary area of epoch B) / mean pupillary area of epoch A.

(Where the mean pupillary area for each individual per epoch is illustrated in table A5.1).

The following table illustrates the relative response amplitude for each participant for each group, between epoch A and epoch B.

	RELATIVE RESPONSE AMPLITUDE		
PARTICIPANT	AD	OLDER ADULT	YOUNGER ADULT
1	0.0116959	0.0332103	- 0.080827
2	- 0.1288	- 0.0633116	- 0.236693
3	- 0.04117	- 0.0714806	0.0746561
4	0.0943775	- 0.036199	- 0.3801324
5	0.0940721	0.0087829	0.1056572
6	0.0104961	0.088983	- 0.0441176
7	0.1803874	0.0696761	- 0.06315
8	0.138221	- 0.0386473	- 0.0965092
9	- 0.1284403	- 0.1056338	- 0.0096153
10	- 0.0373647	- 0.0916666	- 0.1775614
11	0.3432203	- 0.3072139	0.1290322
12	0.0651341	0.0020533	- 0.0332103
	Mean = 0.0501524 sd = 0.128	Mean = - 0.0426206 sd = 0.099	Mean = - 0.0677058 sd = 0.139

TABLE A5.6

Participant	(A) Pupil area at 5 secs (square mm)	(B) area of maximum pupil constriction (square mm)	amplitude of constriction (A-B) (square mm)	1/3 of amplitude constriction (square mm)	(D) time to 1/3 amplitude (after 5 secs)
AD					
1	6.28	5.01	1.27	0.43	0.47
2	13.47	6.7	6.77	2.25	0.45
3	8.93	5.73	3.2	1.06	0.45
4	4.73	3.6	1.08	0.36	0.53
5	8.05	5.4	2.65	0.89	0.62
6	10.62	6.83	3.79	1.27	0.54
7	7.31	5.77	1.54	0.52	0.55
8	6.47	5.5	0.97	0.33	0.75
9	10.94	5.95	4.99	1.66	0.8
10	9.98	7.87	2.11	0.71	0.5
11	4.24	3.33	0.91	0.31	0.47
12	28.35	27.12	1.23	0.41	1.83
Mean	9.947	7.41	2.54	0.85	0.6633
sd	6.1	6.06	1.77	0.59	0.37

TABLE A5.7

Participant	(A) Pupil area at 5 secs (square mm)	(B) area of maximum pupil constriction (square mm)	amplitude of constriction (A-B) (square mm)	1/3 of amplitude constriction (square mm)	(D) time to 1/3 amplitude (after 5 secs)
OLD					
1	8.04	5.13	2.91	0.97	0.47
2	6.07	3.62	2.45	0.81	0.47
3	12.94	10.09	2.85	0.95	0.47
4	6.18	4.65	1.53	0.51	0.4
5	16.28	9.06	7.22	2.4	0.46
6	7.23	4.18	3.05	1.01	0.45
7	9.93	5.99	3.94	1:31	0.5
8	8.34	5.78	2.56	0.85	0.55
9	5.39	3.22	2.17	0.72	0.55
10	17.4	11.37	6.03	2.01	0.5
11	8.29	6.62	1.67	0.55	0.6
12	9.24	5.98	3.26	1.086	0.4
Mean	9.61	6.31	3.3	1.098	0.485
sd	3.76	2.47	1.63	0.54	0.057

TABLE A5.8

Participant	(A) Pupil area at 5 secs (square mm)	(B) area of maximum pupil constriction (square mm)	amplitude of constriction (A-B) (square mm)	1/3 of amplitude constriction (square mm)	(D) time to 1/3 amplitude (after 5 secs)
YOUNG					
1	16.03	10.52	5.51	1.836	0.43
2	8.55	7.01	1.54	0.515	0.47
3	9.53	7.01	2.52	0.84	0.5
4	7.78	4.77	3.01	1.005	0.43
5	11.89	6.76	5.13	1.71	0.4
6	21.45	15.38	6.07	2.025	0.5
7	13.56	7.89	5.67	1.89	0.47
8	9.67	5.46	4.21	1.405	0.4
9	16.14	9.13	7.01	2.335	0.4
10	20.44	10.11	10.33	3.445	0.5
11	9.21	5.56	3.65	1.215	0.47
12	13.77	8.26	5.51	1.835	0.5
Mean	13.17	8.16	5.01	1.67	0.4558
sd	4.4	2.78	2.2	0.74	0.039

TABLE A5.9

Illustrating the speed of the pupillary reflex during the first 1/3 of its total amplitude.

SPEED (mm^2/sec)			
Participant	AD GROUP	OLDER ADULTS	YOUNGER ADULTS
1	0.9148	2.0638	4.2697
2	5.0	1.7234	1.0957
3	2.3555	2.0212	1.68
4	0.6792	1.275	2.3372
5	1.4354	5.1273	4.275
6	2.3518	2.2444	4.05
7	0.9454	2.62	4.0212
8	0.44	1.5454	3.5125
9	2.075	1.3090	5.8375
10	1.42	4.02	6.89
11	0.6595	0.9166	2.5851
12	0.2240	2.715	3.67
MEAN	1.5417	2.3059	3.6853
sd	1.3	1.23	1.64

TABLE 5. 10 INDICATING THE PUPILLARY AREA (in square mm) OF THE 6 RIGHT EYES

	RIGHT EYE	GROUP		
EPOCH	PARTICIPANT	AD	OLDER ADULT	YOUNG ADULT
1 (4 to 5 secs)	1	9.27	8.12	16.65
	2	4.94	6.25	8.62
	3	8.00	6.43	10.06
	4	11.05	16.82	22.10
	5	7.91	10.50	13.70
	6	11.74	8.45	9.74
		mean = 8.82 sd = 2.24	mean = 9.43 sd = 3.59	mean = 13.48 sd =4.72
2 (6 to 7 secs)	1	5.97	5.42	11.65
	2	3.91	3.86	7.33
	3	5.77	5.03	7.54
	4	7.57	9.69	17.28
	5	5.92	6.69	8.39
	6	10.60	6.31	5.99
		mean = 6.62 sd =2..07	mean = 6.17 sd = 1.82	mean = 9.70 sd = 3.8
3 (14 to 15 secs)	1	7.25	6.4	13.32
	2	4.37	4.87	8.74
	3	6.89	5.69	8.85
	4	9.85	13.19	21.24
	5	6.65	7.41	10.35
	6	11.41	7.19	8.03
		mean = 7.74 sd = 2.28	mean = 7.46 sd = 2.7	mean = 11.75 sd = 4.58
4 (16 to 17 secs)	1	8.87	7.34	16.31
	2	4.84	5.93	10.25
	3	6.73	6.61	9.41
	4	9.97	14.61	23.35
	5	7.25	9.28	12.23
	6	14.05	8.28	10.63
		mean = 8.62 sd = 2.91	mean = 8.67 sd = 2.86	mean = 13.7 sd = 4.86

TABLE 5.11 INDICATING THE PUPILLARY AREA (in square mm) OF THE 6 LEFT EYES

	LEFT EYE	GROUP		
EPOCH	PARTICIPANT	AD	OLDER ADULT	YOUNG ADULT
1 (4 to 5 secs)	1	10.30	14.52	7.86
	2	4.22	7.58	9.13
	3	6.11	7.43	9.76
	4	11.44	4.36	10.37
	5	7.05	11.00	13.02
	6	11.49	9.17	5.69
		mean = 8.44	mean = 9.01	mean = 9.31
		sd = 2.79	sd = 3.17	sd = 2.24
2 (6 to 7 secs)	1	7.38	8.96	4.78
	2	3.40	4.84	6.12
	3	4.55	5.79	5.67
	4	8.31	3.12	7.46
	5	6.61	8.78	9.38
	6	11.61	7.31	3.63
		mean = 6.97	mean = 6.47	mean = 6.17
		sd = 2.65	sd = 2.1	sd = 1.85
3 (14 to 15 secs)	1	9.11	9.43	7.16
	2	2.97	6.39	8.11
	3	5.17	6.35	7.99
	4	11.2	3.7	9.59
	5	6.12	9.85	12.12
	6	10.59	8.49	5.53
		mean = 7.53	mean = 7.37	mean = 8.42
		sd = 2.99	sd = 2.12	sd = 2.05
4 (16 to 17 secs)	1	9.52	12.1	8.63
	2	4.31	7.33	9.38
	3	5.66	7.31	8.78
	4	11.53	4.56	10.92
	5	7.26	11.44	14.36
	6	12.19	8.91	5.97
		mean = 8.41	mean = 8.61	mean = 9.67
		sd = 2.91	sd = 2.58	sd = 2.55